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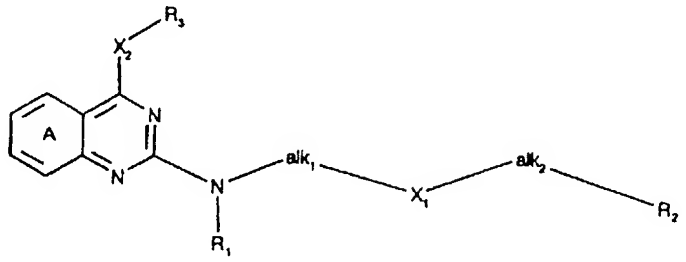

(I)

(57) Abstract

The invention relates to a compound of formula (I) in which the variables are as defined and/or a salt or a tautomer thereof; and relates to a method of treatment of disorders or diseases associated with NPY receptor subtype Y5, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and to the manufacture of the compounds of formula (I) or a salt thereof.

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RECEPTOR ANTAGONISTS

Background of the Invention

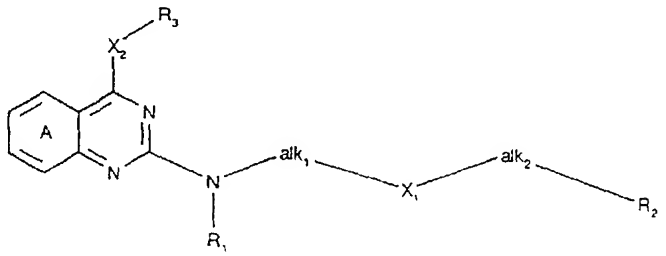
Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family of peptides and is one of the most abundant and widely distributed peptides at the central and peripheral nervous system. NPY acts as a neurotransmitter playing an important role in the regulation of various diseases. Intensive evaluations lead to the finding that multiple NPY receptors are existing being responsible for different physiological and pharmacological activities. Recently, a new NPY receptor subtype has been characterized and cloned, designated as Y5 receptor. It has been demonstrated that the pharmacological function associated with Y5 relates, for example, to obesity and eating disorders. Accordingly, the provision of compounds which act as antagonists of this receptor subtype represents a promisable approach in the regulation of diseases or disorders, such as obesity and eating/food intake disorders.

Summary of the Invention

The invention relates to new compounds having Y5 antagonistic properties, to pharmaceutical compositions and to a method of treatment and prophylaxis of disorders and diseases associated with NPY receptor subtype Y5.

Detailed Description of the Invention

The invention relates to a compound of formula (I)



in which

alk_1 and alk_2, independently of one another, represent, a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, lower alkynyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, nitro, cyano, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, by lower alkoxy, by amino, by substituted amino, by carboxy, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, by carbamoyl, or by N-substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, aminocarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula -X_3(X_4)(X_5) wherein, (a) if X_3 is -CH-, X_4 together with X_5 represent a structural element of formula -X_6-$(CO)_p$-$(CH_2)_o$-, -$(CH_2)_q$-X_6-$(CO)_p$-$(CH_2)_r$-, or -$(CH_2)_s$-X_6-CO-$(CH_2)_t$-; or, (b) if X_3 is -N-, X_4 together with X_5 represent a structural element of formula -CO-$(CH_2)_u$-; [X_6 being -CH_2-, -N(R_1)- or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from -CH_2-;];

X_1 represents C_3-C_8-cycloalkylene, C_3-C_8-cycloalkenylene, C_3-C_8-cycloalkylidene, C_3-C_8-cycloalkenylidene, oxo-C_3-C_8-cycloalkylene, oxo-C_3-C_8-cycloalkenylene, oxo-C_3-C_8-cycloalkylidene, or oxo-C_3-C_8-cycloalkenylidene;

X_2 represents -O-, -$S(O)_n$- or a group of the formula -$N(R_4)$-;

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, N-substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, lower alkenyl, lower alkynyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, lower alkynyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, (carbocyclic or heterocyclic) aroyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, the substituted amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen, lower alkyl, lower alkenyl, lower alkinyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_2-R$, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy; or a salt or a tautomer thereof; and relates to a method of treatment of associated with NPY receptor subtype Y5, to pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and to the manufacture of the compounds of formula (I) or a salt thereof.

Compounds of formula (I) in which X_2-R_3 represent -OH or -SH, are present in form of proton tautomers i.e. in a kind of enol-keto tautomeric forms. Corresponding tautomers also are an embodiment of the present invention.

The compounds (I) can be present as salts, in particular pharmaceutically acceptable salts. If the compounds (I) have, for example, at least one basic centre, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as C_1-C_4- alkanecarboxylic acids which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic

or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, for example aspartic or glutamic acid, or such as benzoic acid, or with organic sulfonic acids, such as C_1-C_4-alkane- or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methane- or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic centre. The compounds (I) having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropylamine, or a mono-, di- or trihydroxy lower alkylamine, for example mono-, di- or triethanolamine. Corresponding internal salts may furthermore be formed, if a compound of formula comprises e.g. both a carboxy and an amino group. Salts which are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds (I) or their pharmaceutically acceptable salts, are also included.

(Carbocyclic or heterocyclic) aryl in (carbocyclic or heterocyclic) aryl or aryloxy, respectively, represents, for example, phenyl, biphenylyl, naphthyl or an appropriate 5- or 6-membered and monocyclic radical or an appropriate bicyclic heteroaryl radical which, in each case, have up to four identical or different hetero atoms, such as nitrogen, oxygen or sulfur atoms, preferably one, two, three or four nitrogen atoms, an oxygen atom or a sulfur atom. Appropriate 5-membered heteroaryl radicals are, for example, monoaza-, diaza-, triaza-, tetraaza-, monooxa- or monothia-cyclic aryl radicals, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl and thienyl, while suitable appropriate 6-membered radicals are in particular pyridyl. Appropriate bicyclic heterocyclic aryls are, for example, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isoquinolinyl, or quinazolinyl. Appropriate aromatic radicals, including ring A, are radicals which may be monosubstituted or polysubstituted, for example di- or trisubstituted, for example by identical or different radicals, for example selected from the group as given above. Preferred substituents of corresponding aryl radicals (including of ring A) are, for example, halogen, lower alkyl, halo-

lower alkyl, lower alkoxy, oxy-lower alkylene-oxy, hydroxy, hydroxy-lower alkoxy, and lower alkoxy-lower alkoxy.

(Carbocyclic or heterocyclic) aroyl is in particular benzoyl, naphthoyl, furoyl, thenoyl, or pyridoyl.

(Carbocyclic or heterocyclic) aryl-lower alkanoyl in (carbocyclic or heterocyclic) aryl-lower alkanoyloxy or (carbocyclic or heterocyclic) aryl -lower alkanoyl is in particular phenyl-lower alkanoyl, naphthyl-lower alkanoyl, or pyridyl-lower alkanoyl,

(Carbocyclic or heterocyclic) aryl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-lower alkyl.

(Carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl is in particular phenyl-, naphthyl- or pyridyl-lower alkoxy.

(Carbocyclic or heterocyclic) arylene represents, in particular, phenylene, naphthylene, thiophenylene, furylene, pyridylene which may be substituted, for example, as indicated for benzo ring A or preferably unsubstituted.

Lower alkyl which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl, amino-lower alkyl, or N- or N,N- substituted amino-lower alkyl.

An amino group which is mono-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl is in particular lower alkylamino, C_3-C_8-cycloalkyl-amino, C_3-C_8-cycloalkyl-loweralkyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-amino, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkylamino.

An amino group which is, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or

heterocyclic) aryl-lower alkyl is in particular di-lower alkylamino, di-C_3-C_8-cycloalkyl-amino, di-(C_3-C_8-cycloalkyl-lower alkyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino, lower alkyl-C_3-C_8-cycloalkyl-amino, lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-amino, lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino.

Lower alkyl which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0, the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, -SO_3H, -SO_2-R and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, lower alkoxy-lower alkoxy-carbonyl-lower alkyl, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl, carbamoyl-lower alkyl, or corresponding N- or N,N-substituted carbamoyl-lower alkyl.

Lower alkoxy which substituted by halogen, hydroxy, lower alkoxy, (carbocyclic or heterocyclic) aryloxy, (carbocyclic or heterocyclic) aryl, or amino is in particular halo-lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl, phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy, amino-lower alkoxy, or corresponding N- or N,N- substituted amino-lower alkoxy.

Lower alkoxy which is substituted by carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, carbamoyl in which the amino group is mono-substituted or, independently of one another, di-substituted by lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, and carbamoyl in which the amino group is di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$, NR_0,

the integer n being 0, 1 or 2 and R_0 being hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl, lower alkanoyl, (carbocyclic or heterocyclic) aroyl, $-SO_3H$, $-SO_2-R$ and R being lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, or (carbocyclic or heterocyclic) aryl-lower alkyl] is in particular carboxy-lower alkoxy, lower alkoxy-carbonyl-lower alkoxy, lower alkoxy-lower alkoxy-carbonyl-lower alkoxy, (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy, carbamoyl-lower alkoxy, N- or N,N-substituted carbamoyl-lower alkoxy.

Substituted lower alkyl or lower alkoxy, respectively, is mono- or poly-substituted, e.g. di- or tri-substituted.

The group of formula $-N(R_3)(R_4)$ [X_2 = $-N(R_4)-$] in which R_3 and R_4 together represent lower alkylene which is condensedat two adjacent carbon atoms with a benzene ring represents, for example, lower alkylene-phenylene-lower alkylene-amino, such as 3,4-dihydro-1*H*-isoquinolin-2-yl.

The general definitions used above and below, unless defined differently, have the following meanings:

The expression "lower" means that corresponding groups and compounds, in each case, in particular comprise not more than 7, preferably not more than 4, carbon atoms.

Halogen is in particular halogen of atomic number not more than 35, such as fluorine, chlorine or bromine, and also includes iodine.

Lower alkyl is in particular C_1-C_7- alkyl, for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, and also includes corresponding pentyl, hexyl and heptyl radicals. C_1-C_4-alkyl is preferred.

Lower alkenyl is in particular C_3-C_7-alkenyl and is, for example, 2-propenyl or 1-, 2- or 3-butenyl. C_3-C_5-alkenyl is preferred.

Lower alkynyl is in particular C_3-C_7-alkynyl and is preferably propargyl.

Lower alkoxy is in particular C_1-C_7-alkoxy and is, for example, methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy, isobutyloxy, sec-butyloxy, tert-butyloxy and also includes corresponding pentyloxy, hexyloxy and heptyloxy radicals. C_1-C_4-alkoxy is preferred.

Lower alkenyloxy is in particular C_3-C_7-alkenyloxy, preferably allyloxycarbonyl, while lower alkynyloxy is in particular C_3-C_5-alkynyloxy, such as propargyloxy.

Oxy-lower alkylene-oxy is in particular oxy-C_1-C_4-alkylene-oxy, preferably oxy-methylene-oxy or oxy-ethylene-oxy.

Lower alkanoyl is in particular C_2-C_7-alkanoyl, such as acetyl, propionyl, butyryl, isobutyryl or pivaloyl. C_2-C_5-alkanoyl is preferred.

Lower alkanoyl-oxy is in particular C_2-C_7-alkanoyl-oxy, such as acetyl-oxy, propionyl-oxy, butyryl-oxy, isobutyryl-oxy or pivaloyl-oxy. C_2-C_5-alkanoyl-oxy is preferred.

Naphthoyl is 1- or 2-naphthoyl, furoyl 2- or 3-furoyl, thenoyl 2- or 3-thenyl, and pyridoyl 2-, 3-, or 4-pyridoyl.

C_3-C_8-Cycloalkyl is, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

C_3-C_8-Cycloalkyl-lower alkyl is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkyl, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkyl. Preferred is cyclopropylmethyl, cyclopentylmethyl or cyclohexylmethyl.

C_3-C_8-Cycloalkoxy is, for example, cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and cycloheptyloxy. Cyclopentyloxy and cyclohexyloxy are preferred.

C_3-C_8-Cycloalkyl-lower alkoxy is in particular C_3-C_8-cycloalkyl-C_1-C_4-alkoxy, in particular C_3-C_6-cycloalkyl-C_1-C_2-alkoxy. Preferred is cyclopropylmethoxy, cyclopentylmethoxy or cyclohexylmethoxy.

C_3-C_8-Cycloalkylene is, for example, C_3-C_6-cycloalkylene, such as 1,3-cyclopentylene, 1,3- or 1,4-cyclohexylene, or 1,4-.

C_3-C_8-Cycloalkenylene is, for example, C_3-C_6-cycloalkenylene, such as 1,3-cyclopent-2-enylene, 1,3- or 1,4-cyclohex-2-enylene.

C_3-C_8-Cycloalkylidene is, for example, C_3-C_6-cycloalkylidene, such as cyclopentylidene, cyclopentylidene or cyclohexylidene.

C_3-C_8-Cycloalkenylidene is, for example, C_3-C_6-cycloalkenylidene, such as 1,1-cyclopent-2-enylidene, 1,1-cyclohex-2-enylidene or 1,1-cyclohex-3-enylidene.

Oxo-C_3-C_8-cycloalkylene is, for example, oxo-C_3-C_6-cycloalkylene, such as 2-oxo-1,3-cyclopentylene, 2-oxo-1,3- or 2-oxo-1,4-cyclohexylene or 3-oxo-1,3- or 3-oxo-1,4-cyclohexylene.

Oxo-C_3-C_8-cycloalkenylene is, for example, oxo-C_3-C_6-cycloalkenylene, such as 2-oxo-1,3-cyclopent-5-enylene, 2-oxo-1,3- or 2-oxo-1,4-cyclohex-5-enylene, or 3-oxo-1,4-cyclohex-5-enylene.

Oxo-C_3-C_8-cycloalkylidene is, for example, oxo-C_3-C_6-cycloalkylidene, such as 2-oxo-1,1-cyclopent-5-enylidene, 2-oxo-1,3- or 2-oxo-1,4-cyclohexenylidene or 3-oxo-1,3- or 3-oxo-1,4-cyclohex-5-enylidene.

Oxo-C_3-C_8-cycloyalkenylidene is, for example, oxo-C_3-C_6-cycloyalkenylidene, such as 2-oxo-1,1-cyclopent-3-enylidene or 2- or 3-oxo-1,1-cyclohex-5-enylidene.

Lower alkylene is in particular C_1-C_7-alkylene, in particular C_1-C_5-alkylene, and is straight-chain or branched and is in particular methylene, ethylene, propylene and butylene and also 1,2-propylene, 2-methyl-1,3-propylene, 3-methyl-1,5-pentylene

and 2,2-dimethyl-1,3-propylene. C_3-C_5-alkylene is preferred. In case of alk_1 or alk_2, respectively, lower alkylene preferably is $-(CH_2)_p-$ the integer p being 1-3. Lower alkylene in an substituted amino group preferably is 1,2-ethylene, 1,3-propylene, 1,4-butylene, 1,5-pentylene, 1,6-hexylene, 2-methyl-1,3-propylene, or 2-methyl-butylene, or 3-methyl-1,5-pentylene.

Amino which is di-substituted by lower alkylene is in particular C_3-C_7-alkyleneamino, preferably 1-azidino, 1-pyrrolidino or 1-piperidino.

Amino which is di-substituted by lower alkylene which is interrupted by O, $S(O)_n$ or NR_0 is in particular morpholino, thiomorpholino or the mono- or di-oxide thereof, or 4-R_0-piperazino.

Lower alkanesulfonyl is in particular C_1-C_4-alkoxy-C_1-C_5-alkoxycarbonyl, preferably ethoxyethoxycarbonyl, methoxyethoxycarbonyl and isopropyloxyethoxycarbonyl.

Lower alkoxycarbonyl is in particular C_2-C_8-alkoxycarbonyl and is, for example, methoxy-, ethoxy-, propyloxy- or pivaloyloxy-carbonyl. C_2-C_5-alkoxycarbonyl is preferred.

Lower alkoxy-lower alkoxy-carbonyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl and is, for example, methoxy- or ethoxy-ethoxy-alkoxycarbonyl.

Hydroxy-lower alkyl is in particular hydroxy-C_1-C_4-alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl. Furthermore, hydroxy-lower alkyl may exhibit two hydroxy groups, such as 3-hydroxy-1-hydroxymethyl-propyl.

Hydroxy-lower alkoxy is in particular hydroxy-C_1-C_4-alkoxy, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy-lower alkoxy is in particular C_1-C_4-alkoxy-C_1-C_4-alkoxy and is, for example, (m)ethoxymethoxy, 2-methoxyethoxy, 2-ethoxyethoxy, 2-n-propyloxyethoxy or ethoxymethoxy.

Amino which is di-substituted by lower alkylene and is condensed at two adjacent carbon atoms with a benzene ring is in particular C_2-C_6-cycloalkylenemino which is condensed at two adjacent carbon atoms with a benzene ring. Preferred is indolin-1-yl or 1,2,3,4-tetrahydro-quinolin-1-yl.

Halo-lower alkyl is in particular halo-C_1-C_4-alkyl, such as trifluoromethyl, 1,1,2-trifluoro-2-chloroethyl or chloromethyl.

Halo-lower alkoxy is in particular halo-C_1-C_4-alkoxy, such as trifluoromethoxy, 1,1,2-trifluoro-2-chloroethoxy or chloromethoxy.

Phenyloxy-, naphthyloxy- or pyridyloxy-lower alkyl is in particular phenyloxy-, naphthyloxy- or pyridyloxy-C_1-C_4-alkyl, such as phenoxy-methyl, 2-phenoxy-ethyl, 1- or 2-naphthyloxy-methyl, or 2-, 3-, or 4-pyridyloxy-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkyl, such as phenyl-methyl, 2-phenyl-ethyl, 1- or 2-naphthyl-methyl, or 2-, 3-, or 4-pyridyl-methyl.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkoxy is in particular phenyl-, naphthyl- or pyridyl-C_1-C_4-alkoxy, such as phenyl-methoxy, 2-phenyl-ethoxy, 1- or 2-naphthyl-methoxy, or 2-, 3-, or 4-pyridyl-methoxy.

Naphthyl is in particular 1- or 2-naphthyl; furyl 2- or 3-furyl; thienyl 2- or 3-thienyl; pyridyl 2-, 3- or 4-pyridyl, indolyl e.g. 1-, 2-, 3- or 5-indolyl, indazolyl e.g. 6-1(H)-indazolyl, benzofuryl e.g. 2-, 3- or 5-benzofuranyl, benzothienyl e.g. 2-, 3-, or 5-benzothienyl, benzimidazolyl e.g. 1-, 2- or 5-benzimidazolyl, quinolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinolinyl, isoquinolinyl e.g. 1-, 3-, 4-, or 6-isoquinolyl, or quinazolinyl e.g. 2-, 4-, 5-, 6-, 7-, or 8-quinazolinyl.

Amino-lower alkyl is in particular amino-C_1-C_7-alkyl, preferably amino-C_1-C_4-alkyl, such as aminomethyl, 2-aminoethyl or 3-aminopropyl.

Lower alkylamino is in particular C_1-C_7-alkylamino and is, for example, methyl-, ethyl-, n-propyl- and isopropyl-amino. C_1-C_4-alkylamino is preferred.

C_3-C_8-Cycloalkyl-amino is in particular C_3-C_6-cycloalkyl-amino and is, for example, cyclopropyl-, cyclopentyl- and cyclohexyl-amino.

C_3-C_8-Cycloalkyl-lower alkylamino is in particular C_3-C_8-cycloalkyl-C_1-C_7-alkylamino and is, for example, cyclopropylmethyl-amino or cyclohexylmethyl-amino. C_3-C_8-Cycloalkyl-C_1-C_4-alkylamino is preferred.

Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl-amino is in particular phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl-amino, preferably benzyl-amino, 2-phenethyl-amino, 1- or 2-naphthylmethyl-amino, or 2-, 3-, or 4-pyridylmethyl-amino.

Di-lower alkylamino is in particular di-C_1-C_4-alkylamino, such as dimethyl-, diethyl-, di-n-propyl-, methylpropyl-, methylethyl-, methylbutyl-amino and dibutylamino.

Di-C_3-C_8-cycloalkyl-amino is in particular di-C_3-C_6-cycloalkylamino, preferably cyclopropylamino, cyclopentylamino or cyclohexylamino.

Di-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular di-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)-amino, preferably cyclopropylmethyl-amino, cyclopentylmethyl-amino or cyclohexylmethyl-amino.

Di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular di-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4- alkyl)-amino, preferably di-benzyl-amino, di-(2-phenethyl)-amino, di-(1- or 2-naphthylmethyl)-amino, or di-(2-, 3-, or 4-pyridylmethyl)-amino.

Lower alkyl-C_3-C_8-cycloalkyl-amino is in particular C_1-C_4-alkyl-C_3-C_6-cycloalkyl-amino, preferably methyl-cyclopropyl-amino, methyl-cyclopentyl-amino or methyl-cyclohexyl-amino.

Lower alkyl-(C_3-C_8-cycloalkyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(C_3-C_6-cycloalkyl-C_1-C_4-alkyl)amino, preferably methyl-cyclopropylmethyl-amino, methyl-cyclopentylmethyl-amino or methyl-cyclohexylmethyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)- amino, such as (m)ethyl-phenyl-amino.

Lower alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-lower alkyl)-amino is in particular C_1-C_4-alkyl-(phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl-C_1-C_4-alkyl)-amino, such as (m)ethyl-benzyl-amino or (m)ethyl-(2-phenethyl)-amino.

Carboxy-lower alkyl is in particular carboxy-C_1-C_4-alkyl, such as carboxy-methyl, 2-carboxy-ethyl, or 3-carboxy-propyl.

Lower alkoxy-carbonyl-lower alkyl is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as (m)ethoxycarbonyl-methyl, 2-(m)ethoxycarbonyl-ethyl or 2-pivaloyl-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkyl is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as 2-methoxy-ethoxycarbonyl-methyl or 2-(2-ethoxy-ethoxycarbonyl)-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkyl is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkyl, such as benzyloxycarbonyl-methyl or 2-(2-phenethyloxy-carbonyl)-ethyl.

Carbamoyl-lower alkyl is in particular carbamoyl-C_1-C_4-alkyl, such as carbamoyl-methyl, 2-carbamoyl-ethyl or 3-carbamoyl-propyl.

Amino-lower alkoxy is in particular amino-C_1-C_4-alkoxy, such as aminomethoxy, 2-aminoethoxy, or 3-amino-propoxy.

Carboxy-lower alkoxy is in particular carboxy-C_1-C_4-alkoxy, such as carboxy-methoxy, 2-carboxy-ethoxy, or 3-carboxy-propyloxy.

Lower alkoxy-carbonyl-lower alkoxy is in particular C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxycarbonyl-methoxy, 2-methoxycarbonyl-ethyl, or 2-(2-ethoxycarbonyl)-ethyl.

Lower alkoxy-lower alkoxy-carbonyl-lower alkoxy is in particular C_1-C_4-alkoxy-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as (m)ethoxymethoxycarbonyl-methoxy, 2-ethoxy-methoxycarbonyl-ethyl, or 2-[(2-ethoxy-ethoxycarbonyl)]-ethyl.

(Phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-lower alkoxycarbonyl-lower alkoxy is in particular (phenyl-, naphthyl-, furyl-, thienyl-, or pyridyl)-C_2-C_5-alkoxycarbonyl-C_1-C_4-alkoxy, such as benzyloxycarbonyl-methoxy, phenethyloxycarbonyl-methoxy, 2-(benzyloxycarbonyl)-ethoxy, or 2-(2-phenethyloxycarbonyl)-ethoxy.

Carbamoyl-lower alkoxy is in particular carbamoyl-C_1-C_4-alkoxy, such as carbamoyl-methoxy, 2-carbamoyl-ethoxy, or 3-carbamoyl-propyloxy.

Obesity, for example, is a wide-spread phenomena which e.g. causes a variety of pathological symptoms or influences the overall state of health. Also associated therewith are considerable socio-economic investments and a heavy financial burden for managed health care organisations. The problem to be solved is to present an approach to systemically treat obesity or related diseases or disorders. Surprisingly, it has been manifested that the modulation of the NPY receptor subtype Y5 leads to a control of the eating behavior.

Extensive pharmacological investigations have shown that the compounds (I) and their pharmaceutically acceptable salts, for example, are useful as antagonists of the neuropeptide Y5 receptor subtype.

Neuropeptide Y (NPY) is a member of the pancreatic polypeptide family with wide-spread distribution throughout the mammalian nervous system. NPY and its relatives (peptide YY or PYY, and pancreatic polypeptide or PP) elicit a broad range of physiological effects through activation of at least five G protein-coupled receptor subtypes known as Y1, Y2, Y3, Y4 (or PP), and the "atypical Y1". The role of NPY as the most powerful stimulant of feeding behavior yet described is thought to occur primarily through activation of the hypothalamic "atypical Y1" receptor. This receptor is unique in that its classification is based solely on feeding behavior data, rather than radioligand binding data, unlike the Y1, Y2, Y3, and Y4 (or PP) receptors, each of which are described previously in both radioligand binding and functional assays. ^{125}I-PYY-

based expression cloning technique may be used to isolate a rat hypothalamic cDNA encoding an "atypical Y1" receptor referred to herein as the Y5 subtype. Y5 homolog may be isolated and characterized of from human hippocampus. Protein sequence analysis reveals that the Y5 receptor belongs to the G protein- coupled receptor superfamily. Both the human and rat homolog display $\leq$ 42% identity in transmembrane domains with the previously cloned "Y-type" receptors. Rat brain localization studies using in situ hybridization techniques verify the existence of Y5 receptor mRNA in rat hypothalamus. Pharmacological evaluation reveals the following similarities between the Y5 and the "atypical Y1" receptor. 1) Peptides bind to the Y5 receptor with a rank order of potency identical to that described for the feeding response: NPY ^{3} NPY_{2-36} = PYY = [Leu^{31}, Pro^{34}]NPY >> NPY_{13-36}. 2) The Y5 receptor is negatively coupled to cAMP accumulation, as has been proposed for the "atypical Y1" receptor. 3) Peptides activate the Y5 receptor with a rank order of potency identical to that described for the feeding response. 4) The reported feeding "modulator" [D-Trp^{32}]NPY binds selectively to the Y5 receptor and subsequently activated the receptor. 5) Both the Y5 and the "atypical Y1" receptors are sensitive to deletions or modifications in the midregion of NPY and related peptide ligands.

The peptide neurotransmitter neuropeptide Y (NPY) is a 36 amino acid member of the pancreatic polypeptide family with widespread distribution throughout the mammalian nervous system. NPY is considered to be the most powerful stimulant of feeding behavior yet described (Clark, J.T., Kalra, P.S., Crowley, W.R., and Kalra, S.P. (1984). Neuropeptide Y and human pancreatic polypeptide stimulate feeding behavior in rats. Endocrinology 115: 427-429, 1984; Levine, A.S., and Morley, J.E. (1984). Neuropeptide Y: A potent inducer of consummatory behavior in rats. Peptides 5: 1025-1029; Stanley, B.G., and Leibowitz, S.F.; (1984) Neuropeptide Y: Stimulation of feeding and drinking by injection into the paraventricular nucleus. Life Sci. 35: 2635-2642). Direct injection into the hypothalamus of satiated rats, for example, can increase food intake up to 10-fold over a 4-hour period (Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The role of NPY in normal and abnormal eating behavior, and the ability to interfere with NPY-dependent pathways as a means to appetite and weight control, are areas of great interest in pharmacological and pharmaceutical research (Sahu and Kalra, 1993; Dryden, S., Frankish, H., Wang, Q., and Williams, G. (1994). Neuropeptide Y and energy balance: one way ahead for the treatment of obesity? Eur. J. Clin. Invest. 24: 293-308). Any credible means of studying or controlling NPY-dependent feeding behavior, however, must

necessarily be highly specific as NPY can act through at least 5 pharmacologically defined receptor subtypes to elicit a wide variety of physiological functions (Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167). It is therefore vital that knowledge of the molecular biology and structural diversity of the individual receptor subtypes be understood as part of a rational drug design approach to develop subtype selective compounds. A brief review of NPY receptor pharmacology is summarized below and also in Table 1.

TABLE 1: Pharmacologically defined receptors for NPY and related pancreatic polypeptides.

Rank orders of affinity for key peptides (NPY, PYY, PP, [Leu^{31},Pro^{34}]NPY, NPY_{2-36}, and NPY_{13-36}) are based on previously reported binding and functional data (Schwartz, T.W., J. Fuhlendorff, L.L.Kjems, M.S. Kristensen, M. Vervelde, M. O'Hare, J.L. Krstenansky, and B. Bjornholm. (1990). Signal epitopes in the three-dimensional structure of neuropeptide Y. Ann. N.Y. Acad. Sci. 611: 35-47; Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082; Dumont, Y., J.-C. Martel, A. Fournier, S. St-Pierre, and R. Quirion. (1992). Neuropeptide Y and neuropeptide Y receptor subtypes in brain and peripheral tissues. Progress in Neurobiology 38: 125-167; Wahlestedt, C., and D.J. Reis. (1993). Neuropeptide Y-Related Peptides and Their Receptors--Are the Receptors Potential Therapeutic Targets? Ann. Rev. Pharmacol. Tox. 32: 309-352). Missing peptides in the series reflect a lack of published information.

TABLE 1

Receptor	Affinity (pK_i or pEC_{50})					
	11 to 10	10 to 9	9 to 8	8 to 7	7 to 6	< 6
Y1	NPY PYY [Leu^{31},Pro^{34}] NPY		NPY_{2-36}	NPY_{13-36}	PP	
Y2		PYY NPY NPY_{2-36}	NPY_{13-36}			[Leu^{31}, Pro^{34}] NPY PP
Y3		NPY	[Pro^{34}] NPY	NPY_{13-36}PP		PYY
Y4	PP	PYY [Leu^{31},Pro^{34}] NPY	NPY NPY_{2-36}	NPY_{13-36}		
Y5		PYY NPY NPY_{2-36} [Leu^{31},Pro^{34}] NPY		NPY_{13-36}		

NPY Receptor Pharmacology

NPY receptor pharmacology has historically been based on structure/activity relationships within the pancreatic polypeptide family. The entire family includes the namesake pancreatic polypeptide (PP), synthesized primarily by endocrine cells in the pancreas; peptide YY (PYY), synthesized primarily by endocrine cells in the gut; and NPY, synthesized primarily in neurons (Michel, M.C. (1991). Receptors for neuropeptide Y: multiple subtypes and multiple second messengers. Trends Pharmacol.: 12: 389-394; Dumont et al., 1992; Wahlestedt and Reis, 1993). All pancreatic polypeptide family members share a compact structure involving a "PP-fold" and a conserved C-terminal hexapeptide ending in Tyr^{36} (or Y^{36} in the single letter code). The striking conservation of Y^{36} has prompted the reference to the pancreatic polypeptides' receptors as "Y-type" receptors (Wahlestedt, C., L. Edvinsson, E. Ekblad, and R. Hakanson. Effects of neuropeptide Y at sympathetic neuroeffector junctions: Existence of Y_1 and Y_2 receptors. In: Neuronal messengers in vascular function, Fernstrom Symp. No 10., pp. 231-242. Eds A. Nobin and C.H. Owman. Elsevier: Amsterdam (1987)), all of which are proposed to function as seven transmembrane-spanning G protein-coupled receptors (Dumont et al., 1992).

The Y1 receptor recognizes NPY = PYY >> PP (Grundemar et al., 1992). The receptor requires both the N- and the C-terminal regions of the peptides for optimal recognition. Exchange of Gln^{34} in NPY or PYY with the analogous residue from PP (Pro^{34}), however, is well-tolerated. The Y1 receptor has been cloned from a variety of species including human, rat and mouse (Larhammar, D., A.G. Blomqvist, F. Yee, E. Jazin, H. Yoo, and C. Wahlestedt. (1992). Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. J. Biol. Chem. 267: 10935-10938; Herzog, H., Y.J. Hort, H.J. Ball, G. Hayes, J. Shine, and L. Selbie. (1992). Cloned human neuropeptide Y receptor couples to two different second messenger systems. Proc. Natl. Acad. Sci. USA 89, 5794-5798; Eva, C., Oberto, A., Sprengel, R. and E. Genazzani. (1992). The murine NPY-1 receptor gene: structure and delineation of tissue specific expression. FEBS lett. 314: 285-288; Eva, C., Keinanen, K., Monyer, H., Seeburg, P., and Sprengel, R. (1990). Molecular cloning of a novel G protein-coupled receptor that may belong to the neuropeptide receptor family. FEBS Lett. 271, 80-84). The Y2 receptor recognizes PYY ~ NPY >> PP and is relatively tolerant of N-terminal deletion (Grundemar, L. and RI Hakanson (1994). Neuropeptide Y effector systems:

perspectives for drug development. Trends. Pharmacol. 15:153-159). The receptor has a strict requirement for structure in the C-terminus (Arg^{33}-Gln^{34}-Arg^{35}-Tyr^{36}-NH_2); exchange of Gln^{34} with Pro^{34}, as in PP, is not well tolerated. The Y2 receptor has recently been cloned. The Y3 receptor is characterized by a strong preference for NPY over PYY and PP (Wahlestedt, C., Karoum, F., Jaskiw, G., Wyatt, R.J., Larhammar, D., Ekman, R., and Reis, D.J. (1991). Cocaine-induced reduction of brain neuropeptide Y synthesis dependent on medial prefrontal cortex. Proc. Natl. Acad. Sci. 88: 2978-2082). [Pro^{34}]NPY is reasonably well tolerated even though PP, which also contains Pro^{34}, does not bind well to the Y3 receptor. This receptor (Y3) has not yet been cloned. The Y4 receptor binds PP > PYY > NPY. Like the Y1, the Y4 requires both the N- and the C-terminal regions of the peptides for optimal recognition. The "atypical Y1" or "feeding" receptor is defined exclusively by injection of several pancreatic polypeptide analogs into the paraventricular nucleus of the rat hypothalamus which stimulates feeding behavior with the following rank order: $NPY_{2-36} \geq$ NPY ~ PYY ~ [Leu^{31},Pro^{34}]NPY > NPY_{13-36} (Kalra, S.P., Dube, M.G., Fournier, A., and Kalra, P.S. (1991). Structure-function analysis of stimulation of food intake by neuropeptide Y: Effects of receptor agonists. Physiology & Behavior 50: 5-9; Stanley, B.G., Magdalin, W., Seirafi, A., Nguyen, M.M., and Leibowitz, S.F. (1992). Evidence for neuropeptide Y mediation of eating produced by food deprivation and for a variant of the Y_1 receptor mediating this peptide's effect. Peptides 13: 581-587). The profile is similar to that of a Y1-like receptor except for the anomalous ability of NPY_{2-36} to stimulate food intake with potency equivalent or better than that of NPY. A subsequent report by Balasubramaniam, A., Sheriff, S., Johnson, M.E., Prabhakaran, M., Huang, Y., Fischer, J.E., and Chance, W.T. (1994). [D-Trp^{32}]Neuropeptide Y: A competitive antagonist of NPY in rat hypothalamus. J. Med. Chem. 37: 311-815 showed that feeding can be regulated by [D-Trp^{32}]NPY. While this peptide is presented as an NPY antagonist, the published data at least in part support a stimulatory effect of [D-Trp^{32}]NPY on feeding. [D-Trp^{32}]NPY thereby represents another diagnostic tool for receptor identification.

This plasmid (pcEXV-hY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. 75943.

The plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the rat Y5 receptor as to permit expression thereof has been designated as pcEXV-rY5 (ATCC Accession No. 75944).

This plasmid (pcEXV-rY5) was deposited on November 4, 1994 with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorgansims for the Purposes of Patent Procedure and was accorded ATCC Accession No. CRL 75944.

A method for determining whether a ligand can specifically bind to a Y5 receptor comprises contacting a cell transfected with and expressing DNA encoding the Y5 receptor with the ligand under conditions permitting binding of ligands to such receptor, detecting the presence of any such ligand specifically bound to the Y5 receptor, and thereby determining whether the ligand specifically binds to the Y5 receptor.

A method for determining whether a ligand is a Y5 receptor antagonist comprises contacting a cell transfected with and expressing DNA encoding a Y5 receptor with the ligand in the presence of a known Y5 receptor agonist, such as PYY or NPY, under conditions permitting the activation of a functional Y5 receptor response, detecting a decrease in Y5 receptor activity, and thereby determining whether the ligand is a Y5 receptor antagonist.

In an embodiment of the above-described methods, the cell is non-neuronal in origin. In a further embodiment, the non-neuronal cell is a COS-7 cell, 293 human embryonic kidney cell, NIH-3T3 cell or L-M(TK-) cell.

The cell lines are transfected with a vector which is adapted for expression in a mammalian cell which comprises the regulatory elements necessary for expression of the DNA in the mammalian cell operatively linked to the DNA encoding the mammalian Y5 receptor as to permit expression thereof.

For example, such plasmid which comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to the DNA encoding the human

Y5 receptor as to permit expression thereof designated pcEXV-hY5 (ATCC Accession No. 75943).

Experimental Details

MATERIALS AND METHODS

cDNA Cloning

Total RNA was prepared by a modification of the guanidine thiocyanate method (Kingston, 1987), from 5 grams of rat hypothalamus (Rockland, Gilbertsville, PA). Poly A^+RNA was purified with a FastTrack kit (Invitrogen Corp., San Diego, CA). Double stranded (ds) cDNA was synthesized from 7 mg of poly A^+ RNA according to Gubler and Hoffman (Gubler, U abd B.J. Hoffman. (1983). A simple and very efficient method for generating cDNA libraries. Gene. 25, 263-269), except that ligase was omitted in the second strand cDNA synthesis. The resulting DS cDNA was ligated to BstxI/EcoRI adaptors (Invitrogen Corp.), the excess of adaptors was removed by chromatography on Sephacryl 500 HR (Pharmacia®-LKB) and the ds-cDNA size selected on a Gen-Pak Fax HPLC column (Millipore Corp., Milford, MA). High molecular weight fractions were ligated in pEXJ.BS (A cDNA cloning expression vector derived from pcEXV-3; Okayama, H. and P. Berg (1983). A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. Mol. Cell. Biol. 3: 280-289; Miller, J. and Germain, R.N. (1986). Efficient cell surface expression of class II MHC molecules in the absence of associated invariant chain. J. Exp. Med. 164: 1478-1489) cut by BstxI as described by Aruffo and Seed (Aruffo, A. and Seed, B. (1987). Molecular cloning of a CD28 cDNA by a high efficiency COS cell expression system. PNAS, 84, 8573-8577). The ligated DNA was electroporated in E.Coli MC 1061 F^+ (Gene Pulser, Biorad). A total of 3.4×10^6 independent clones with an insert mean size of 2.7 kb could be generated. The library was plated on Petri dishes (Ampicillin selection) in pools of 6.9 to 8.2×10^3 independent clones. After 18 hours amplification, the bacteria from each pool were scraped, resuspended in 4 ml of LB media and 1.5 ml processed for plasmid purification with a QIAprep-8 plasmid kit (Qiagen Inc, Chatsworth, CA). 1 ml aliquots of each bacterial pool were stored at -85°C in 20% glycerol.

Isolation of a cDNA clone encoding an atypical rat hypothalamic NPY5 receptor

DNA from pools of » 7500 independent clones was transfected into COS-7 cells by a modification of the DEAE-dextran procedure (Warden, D. and H.V. Thorne. (1968). Infectivity of polyoma virus DNA for mouse embryo cells in presence of diethylaminoethyl-dextran. J. Gen. Virol. 3, 371). COS-7 cells were grown in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal calf serum, 100 U/ml of penicillin, 100 mg/ml of streptomycin, 2 mM L-glutamine (DMEM-C) at 37°C in 5% CO_2. The cells were seeded one day before transfection at a density of 30,000 cells/cm^2 on Lab-Tek chamber slides (1 chamber, Permanox slide from Nunc Inc., Naperville, IL). On the next day, cells were washed twice with PBS, 735 ml of transfection cocktail was added containing 1/10 of the DNA from each pool and DEAE-dextran (500 mg/ml) in Opti-MEM I serum free media (Gibco®BRL LifeTechnologies Inc. Grand Island, NY). After a 30 min. incubation at 37°C, 3 ml of chloroquine (80 mM in DMEM-C) was added and the cells incubated a further 2.5 hours at 37°C. The media was aspirated from each chamber and 2 ml of 10% DMSO in DMEM-C added. After 2.5 min. incubation at room temperature, the media was aspirated, each chamber washed once with 2 ml PBS, the cells incubated 48 hours in DMEM-C and the binding assay was performed on the slides. After one wash with PBS, positive pools were identified by incubating the cells with 1 nM ($3x10^6$ cpm per slide) of porcine [^{125}I]-PYY (NEN; SA=2200 Ci/mmole) in 20 mM Hepes-NaOH pH 7.4, CaCl2 1.26 mM, MgSO4 0.81 mM, KH_2PO_4 0.44 mM, KCL 5.4, NaCl 10 mM, .1% BSA, 0.1% bacitracin for 1 hour at room temperature. After six washes (three seconds each) in binding buffer without ligand, the monolayers were fixed in 2.5% glutaraldehyde in PBS for five minutes, washed twice for two minutes in PBS, dehydrated in ethanol baths for two minutes each (70, 80, 95, 100%) and air dried. The slides were then dipped in 100% photoemulsion (Kodak® type NTB2) at 42°C and exposed in the dark for 48 hours at 4°c in light proof boxes containing drierite. Slides were developed for three minutes in Kodak® D19 developer (32 g/l of water), rinsed in water, fixed in Kodak® fixer for 5 minutes, rinsed in water, air dried and mounted with Aqua-Mount (Lerner Laboratories, Pittsburgh, PA). Slides were screened at 25x total magnification. A single clone, CG-18, was isolated by SIB selection as described (Mc Cormick, 1987). DS-DNA was sequenced with a Sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer. Nucleotide and peptide sequence analysis were performed with GCG programs (Genetics Computer group, Madison, WI).

Isolation of the human Y5 homolog

Using rat oligonucleotide primers in TM 3 (sense primer; position 484-509 in SEQ ID NO:1) and in TM 6 (antisense primer; position 1219-1243 in SEQ ID NO: 1), a human hippocampal cDNA library has been screened using the polymerase chain reaction. 1 μl (4×10^6 bacteria) of each of 450 amplified pools containing each »5000 independent clones and representing a total of 2.2×10^5 was subjected directly to 40 cycles of PCR and the resulting products analyzed by agarose gel electrophoresis. One of three positive pools was analyzed further and by sib selection a single cDNA clone was isolated and characterized. This cDNA turned out to be full length and in the correct orientation for expression. DS-DNA was sequenced with a sequenase kit (US Biochemical, Cleveland, OH) according to the manufacturer.

Cell Culture

COS-7 cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37°C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:6 every 3-4 days. Human embryonic kidney 293 cells were grown on 150 mm plates in D-MEM with supplements (minimal essential medium) with Hanks' salts and supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of 293 cells were trypsinized and split 1:6 every 3-4 days. Mouse fibroblast LMT(k)- cells were grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 mg/ml streptomycin) at 37 °C, 5% CO_2. Stock plates of COS-7 cells were trypsinized and split 1:10 every 3-4 days.

Stable Transfection

Human Y5 and rat Y5 receptors were co-transfected with a G-418 resistant gene into mouse fibroblast LMT(k)- cells by a calcium phosphate transfection method (Cullen, B.

(1987). Use of eurkaryotic expression technology in the functional analysis of cloned genes. Methods Enzymol. 152: 685-704). Stably transfected cells were selected with G-418.

EXPERIMENTAL RESULTS

cDNA Cloning

In order to clone a rat hypothalamic "atypical" NPY receptor subtype, applicants used an expression cloning strategy in COS-7 cells (Gearing et al, 1989; Kluxen, F.W., Bruns, C. and Lubbert H. (1992). Expression cloning of a rat brain somatostatin receptor cDNA. Proc. Natl. Acad. Sci. USA 89, 4618-4622; Kieffer, B., Befort, K., Gaveriaux-Ruff, C. and Hirth, C.G. (1992). The
δ-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. Proc. natl. Acad. Sci. USA 89, 12048-12052). This strategy was chosen for its extreme sensitivity since it allows detection of a single "receptor positive" cell by direct microscopic autoradiography. Since the "atypical" receptor has only been described in feeding behavior studies involving injection of NPY and NPY related ligands in rat hypothalamus (see introduction), applicants first examined its binding profile by running competitive displacement studies of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ on membranes prepared from rat hypothalamus. The competitive displacement data indicate: 1) Human PP is able to displace 20% of the bound ^{125}I-PYY with an IC_{50} of 11 nM (Fig. 1 and Table 2). As can be seen in table 5, this value does not fit with the isolated rat Y1, Y2 and Y4 clones and could therefore correspond to another NPY/PYY receptor subtype. 2) [Leu$_{31}$, Pro$_{34}$] NPY (a Y1 specific ligand) is able to displace with high affinity (IC_{50} of 0.38) 27% of the bound ^{125}I-PYY$_{3-36}$ ligand (a Y2 specific ligand) (Fig. 2 and table 2). These data provide the first evidence based on a binding assay that rat hypothalamic membranes could carry an NPY receptor subtype with a mixed Y1/Y2 pharmacology (referred to as the "atypical" subtype) which fits with the pharmacology defined in feeding behavior studies.

TABLE 2: Pharmacological profile of the rat hypothalamus.

Binding data reflect competitive displacement of ^{125}I-PYY and ^{125}I-PYY$_{3-36}$ from rat hypothalamic membranes. Peptides were tested at concentrations ranging from 0.001 nM to 100 nM unless noted. The IC_{50} value corresponding to 50% displacement, and the

percentage of displacement relative to that produced by 300 nM human NPY, were determined by nonlinear regression analysis. Data shown are representative of at least two independent experiments.

TABLE 2

Peptide	IC_{50} Values, nM (% NPY-produced displacement)	
	^{125}I-PYY	^{125}I-PYY$_{3-36}$
human NPY	0.82 (100%)	1.5 (100%)
human NPY$_{2-36}$	2.3 (100%)	1.2 (100%)
human [Leu^{31},Pro^{34}]NPY	0.21 (44%) 340 (56%)	0.38 (27%) 250 (73%)
human PYY	1.3 (100%)	0.29 (100%)
human PP	11 (20%)	untested

Based on the above data, a rat hypothalamic cDNA library of 3 x 10^6 independent recombinants with a 2.7 kb average insert size was fractionated into 450 pools of »7500 independent clones. All pools were tested in a binding assay with ^{125}I-PYY as described (Y2 patent). Seven pools gave rise to positive cells in the screening assay (# 81, 92, 147, 246, 254, 290, 312). Since Y1, Y2, Y4 and Y5 receptor subtypes (by PCR or binding analysis) are expressed in rat hypothalamus, applicants analyzed the DNA of positive pools by PCR with rat Y1, Y2 and Y4 specific primers. Pools # 147, 246, 254 and 312 turned out to contain cDNAs encoding a Y1 receptor, pool # 290 turned out to encode a Y2 subtype, but pools # 81 and 92 were negative by PCR analysis for Y1, Y2 and Y4 and therefore likely contained a cDNA encoding a new rat hypothalamic NPY receptor (Y5). Pools # 81 and 92 later turned out to contain an identical NPY receptor cDNA. Pool 92 was subjected to sib selection as described until a single clone was isolated (designated CG-18).

The isolated clone carries a 2.8 kb cDNA. This cDNA contains an open reading frame between nucleotides 779 and 2146 that encodes a 456 amino acid protein. The long 5' untranslated region could be involved in the regulation of translation efficiency or mRNA stability. The flanking sequence around the putative initiation codon does not conform to the Kozak consensus sequence for optimal translation initiation (Kozak, M. (1989). The scanning model for translation: an update. J. Cell Biol. 108, 229-241; Kozak, M. (1991). Structural features in eukaryotic mRNAs that modulate the initiation of translation. J. Biol. Chem. 266, 19867-19870). The hydrophobicity plot displayed seven hydrophobic, putative membrane spanning regions which makes the rat hypothalamic Y5 receptor a member of the G-protein coupled superfamily. The nucleotide and deduced amino acid sequences are shown in SEQ ID NOS: 1 and 2, respectively.

Localization studies show that the Y5 mRNA is present in several areas of the rat hippocampus. Assuming a comparable localization in human brain, applicants screened a human hippocampal cDNA library with rat oligonucleotide primers which were shown to yield a DNA band of the expected size in a PCR reaction run on human hippocampal cDNA. Using this PCR screening strategy (Gerald et al, 1994, submitted for publication), three positive pools were identified. One of these pools was analyzed further, and an isolated clone was purified by sib selection. The isolated clone (CG-19) turned out to contain a full length cDNA cloned in the correct orientation for functional expression (see below). The human Y5 nucleotide and deduced amino acid sequences are shown in SEQ ID NOS 3 and 4, respectively. When compared to the rat Y5 receptor the human sequence shows 84.1% nucleotide identity and 87.2% amino acid identity. The rat protein sequence is one amino acid longer at the very end of both amino and carboxy tails of the receptor when compared to the rat. Both pharmacological profiles and functional characteristics of the rat and human Y5 receptor subtype homologs may be expected to match closely.

When the human and rat Y5 receptor sequences were compared to other NPY receptor subtypes or to other human G protein-coupled receptor subtypes, both overall and transmembrane domain identities are very low, showing that the Y5 receptor genes are not closely related to any other previously characterized cDNAs.

The compounds according to the present invention and their pharmaceutically acceptable salts have proven to exhibit pronounced and selective affinity to the Y5 receptor subtype

(shown in Y5 binding test) and in vitro and in vivo antagonistic properties. These properties are shown in vitro by their ability to inhibit NPY-induced calcium increase in stable transfected cells expressing the Y5 receptor and in vivo by their ability to inhibit food intake induced by intracerebroventricular application of NPY or 24 h food deprivation in conscious rats.

Binding experiments

The selective affinity of the compounds according to the present invention to the Y5 receptor is detected in a Y5 binding assay using LM(tk-)-h-NPY5-7 cells which stably express the human NPY Y5 receptor or HEK-293 cells stably expressing the rat NPY Y5 receptor.

The following buffers are used for the preparation of membranes and for binding assay:

a) buffer 1 (homogenisation buffer, pH 7.7 at 4°C) contains Tris-HCl [FLUKA, Buchs, Switzerland] (20 mM) and ethylenediamine tetraacetate (EDTA) [FLUKA, Buchs, Switzerland] (5 mM); b) buffer 2 (suspension buffer, pH: 7.4 at room temperature) contains N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) [Boehringer Mannheim, Germany] (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM) and KH_2PO_4 (0.22 mM); buffer 3 (binding buffer, pH 7.4 at room temperature) contains HEPES (20 mM), NaCl (10 mM), $CaCl_2$ (1.26 mM), $MgSO_4$ (0.81 mM), KH_2PO_4 (0.22 mM) and 1 mg/ml bovine serum albumin [FLUKA].

Cells are washed in phosphate buffered saline and harvested using a rubber policeman. The cells are homogenised using a Polytron homogeniser (3 bursts of 8 seconds) in ice-cold hypotonic buffer (buffer 1, pH 7.7 at 4°C). The homogenate is centrifuged at 32,000 x g for 20 min at 4°C. The pellets are resuspended in the same buffer and recentrifuged. The final pellets are suspended in buffer 2. Protein concentration is measured by the method of Bradford using the Pierce reagent [PIERCE, Rockford, USA], with bovine serum albumin as standard. The crude membrane preparation is aliquoted, flash-frozen in liquid nitrogen and stored at -80°C. Before use, 0.1% (1 mg/ml) bovine serum albumin is added.

^{125}I-[Pro^{34}]hPYY (60 pM, Anawa, Wangen, Switzerland) dissolved in buffer 3 is used as radioligand. All test compounds are dissolved in dimethyl sulfoxide (DMSO) at 10^{-2} M and diluted to 10^{-3} M in buffer 3. Subsequent dilutions are in buffer 3 plus 10% DMSO. Incubations are performed in Millipore Multiscreen FC filter plates [Millipore, Bedford, USA]. The filters in each well are pretreated with 2% polyethyleneimine for 30 min and rinsed once with 300 microL buffer 3 before use. The following are pipetted into each well: 20 microL

buffer 3, 25 microL ^{125}I-[Pro^{34}]hPYY [SAXON, Hannover, Germany] (600 pM); 25 microL test compound (or binding buffer for the controls); 180 microL crude membrane suspension (approximately 5 microg protein). Incubations are performed at room temperature for 2h. Non-specific binding is defined as the binding remaining in the presence of 1 microM [Pro^{34}]hPYY. The incubations are terminated by rapid filtration and washing four times with 300microL phosphate buffered saline. The filters are removed from the wells, placed into plastic tubes and assayed for radioactivity in a gamma counter [Gammamaster, WALLAC, Finland].

The IC50 values of the compounds according to this invention at the human Y5 receptor range especially between about 0.1 nM and about 10 microM. Representatives are, for example, the final products of working examples 53, 54, 55, and 88, for which following IC50 values [μM/L] were determined: 0.0023 (Ex. 53); 0.018 (Ex. 54); 0.0017 (Ex. 55); 0.0077 (Ex. 88).

Measurements of calcium transient

For the determination of in vitro antagonistic properties of the compounds according to the present invention, stably transfected LM(tk-)-hY5-7 cells are used in which a NPY-induced calcium transient is measured as described below. Cells are harvested in a medium containing EDTA (0.5 mM) and phosphate buffered saline (PBS). Cells are then washed in phosphate buffered saline solution and loaded for 90 min at room temperature and pH 7.4 with 10 microM FLUO-AM (fluoro-3-acetoxy methylester, supplemented with pluronic acid as suggested by the manufacturer, Molecular Probes Inc., Eugene, Oregon, USA) in a cell culture buffer of the following composition (NaCl 120 mM, $MgCl_2$ 1 mM, KCl 5.4 mM, NaH_4PO_4 0.33 mM, glucose 11 mM, taurine 5 mM, pyruvate 2 mM, glutamine 1.5 mM HEPES 10 mM, insulin 10 U/l, BSA 0.1% at for 90 min at room temperature. After centrifugation the cells are resuspended in the cell culture buffer at a concentration of 3-4 million cells/ml and supplemented with 200 microM sulfinpyrazone.

Calcium transients are measured at room temperature in a millititer plate using a Cytofluor 2350 (Millipore) with wavelength settings at 485 nm for excitation and 530 nm for emission. 180 microL of cells suspension are preincubated in the presence of various amounts of compounds dissolved in 2 microL DMSO in triplicates (or 2 microL DMSO for the controls) for 5 min and then NPY is added at a final concentration of 100 nM. The compound

concentrations giving 50% inhibition of the maximum of the Ca transients are then calculated.

In this cell system, NPY induces Ca transients with an EC50 of 50 nM. The data are analyzed using a Microsoft Excel software. The concentrations which cause a 50% inhibition of the initial control values are given as IC50 values. The IC50 values are determined for the compounds according to the present invention and their pharmaceutically acceptable salts.

The property of the compounds according to the present invention and their pharmaceutically acceptable salts to inhibit NPY-induced increase intracellular calcium indicates their antagonistic properties with IC50 values ranging especially between about 0.1 nM and about 10 microM.

Measurements of NPY-induced food intake in conscious rats

In addition this antagonistic property of the Y5 receptor subtype is also observed in-vivo in conscious rats by their ability to inhibit NPY-induced food intake. For these determinations food intake is measured in normal satiated rats after intracerebroventricular application (i.c.v.) of neuropeptide Y [BACHEM, Feinchemikalien, Bubendorf, Switzerland] in the presence or absence of the compounds according to the present invention. Male Sprague-Dawley rats weighing 180-220 g are used for all experiments. They are individually housed in stainless steel cages and maintained on a 11:13 h light-dark schedule (lights off at 1800 h) under controlled temperature (21-23 °C) at all times. Water and food (NAFAG lab chow pellets) [NAFAG, Gossau, Switzerland] are available ad libitum.

Under pentobarbital [VETERINARIA AB, Zürich, Switzerland] anesthesia, all rats are implanted with a stainless steel guide cannula targeted at the right lateral ventricle. Stereotaxic coordinates, with the incisor bar set -2.0 mm below interaural line, are : -0.8 mm anterior and +1.3 mm lateral to bregma. The guide cannula is placed on the dura. Injection cannulas extended the guide cannulas -3.8 mm ventrally to the skull surface. Animals are allowed at least 4 days of recovery postoperatively before being used in the experiments.

Cannula placement is checked postoperatively by testing all rats for their drinking response to a 50 ng intracerebroventricular (icv) injection of angiotensin II . Only rats which drink at least 2.5 ml of water within 30 min after angiotensin II injection are used in the feeding studies. Injections are made in the morning 2 hours after light onset. Peptides are injected in artificial cerebrospinal fluid (ACSF) [FLUKA, Buchs, Switzerland] in a volume of 5 μl. The ACSF contains NaCl 124 mM, KCl 3.75 mM, $CaCl_2$ 2.5 mM, $MgSO_4$ 2.0 mM, KH_4PO_4 0.22

mM, $NaHCO_3$ 26 mM and glucose 10 mM. NPY (300 pmole) is administered by the intracerebroventricular route 10-60 minutes after administration of compounds or vehicle DMSO/water (10%,v/v) or cremophor/water (20%,v/v) [SIGMA, Buchs, Switzerland].

Food intake is measured by placing preweighed pellets into the cages at the time of NPY injection. Pellets are removed from the cage subsequently at each time point indicated in the figures and replaced with a new set of preweighed pellets.
All results are presented as means ±SEM. Statistical analysis is performed by analysis of variance using Student-Newman-Keuls test.

The compounds according to the present invention inhibit NPY-induced food intake in rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

Measurements of food intake in 24 hours food deprived rats

Based on the observation that food deprivation induces an increase in the hypothalamic NPY levels, it is assumed that NPY mediates food intake induced by food deprivation. Thus, the compounds according to the present invention are also tested in rats after 24 hours food deprivation. These experiments are conducted with male Sprague-Dawley (CIBA-GEIGY AG, Sisseln, Switzerland) rats weighing between 220 and 250 g. The animals are housed in individual cages for the duration of the study and allowed free access to normal food together with tap water. The animals are maintained in room with a 12 h light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the individual cages the rats undergo a 2-4 days equilibration period, during which they are habituated to their new environment and to eating a powdered or pellet diet [NAFAG, Gossau, Switzerland]. At the end of the equilibration period, food is removed from the animals for 24 hours starting at 8.00 a.m. At the end of the fasting period the animals are injected intraperitoneally, intravenously or orally either with the compounds according to the present invention or an equivalent volume of vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v) and 10-60 min later the food is returned to them. Food intake at various time periods is monitored over the following 24 hour period. Inhibition of food intake by the compounds according to the present invention is given in percentage of the respective control vehicle-treated rats.
The compounds according to the present invention inhibit food intake in this food deprived rat model in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal,

subcutaneous or intravenous administration. Representatives are, for example, the final products of working examples 53, 55 and 88, for which an inhibition of food intake of 96% or 87% or 92%, respectively, versus the respective control vehicle-treated animals after i.p. application of 30 mg/kg was determined.

Measurements of food intake in obese Zucker rats

The antiobesity efficacy of the compounds according to the present invention can also be shown in Zucker obese rats, an art-known animal model of obesity. These studies are conducted with male Zucker fatty rats (fa/fa) [HARLAN CPB, Austerlitz, NL] weighing between 480 and 500 g. Animals are individually housed in metabolism cages for the duration of the study and allowed free access to powdered food together with tap water. The animals are maintained in a room with a 12 hour light/dark cycle (8 a.m. to 8.00 p.m. light) at 24°C and monitored humidity. After placement into the metabolism cages the rats undergo a 6 day equilibration period, during which they are habituated to their new environment and to eating a powdered diet. At the end of the equilibration period, food intake during the light and dark phases is determined. After a 3 day control period, the animals are treated with the compounds according to the present invention or vehicle DMSO/water (10%, v/v) or cremophor/water (20%, v/v).

The compounds according to the present invention inhibit food intake in Zucker obese rats in a range especially of about 0.01 to about 100 mg/kg after oral, intraperitoneal, subcutaneous or intravenous administration.

The above experiments clearly demonstrate that the Y5 receptor subtype is the primary mediator of NPY-induced feeding and that corresponding antagonists can be used for the treatment of obesity and related disorders [*Nature, Vol. 382, 168-171 (1996)*].

The compounds according to the present invention can inhibit food intake induced either by intracerebroventricular application of NPY or by food deprivation or as well as spontaneous eating in the Zucker obese rat. Thus, the compounds according to the present invention can especially be used for the prophylaxis and treatment of disorders or diseases associated with the Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine,

sleep disturbance, and pain and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The compounds according to the present invention act as antagonists of neuropeptide Y (NPY) binding at the Y5 receptor subtype. By virtue of their Y5 receptor antagonistic property, the compounds of the formula (I) and their pharmaceutically acceptable salts can therefore be used, for example, as pharmaceutical active ingredients in pharmaceutical compositions which are employed, for example, for the prophylaxis and treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a method of treatment of diseases and disorders associated with NPY Y5 receptor subtype, especially in the prophylaxis and treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea, comprising administering to a warm-blooded animal, including man, in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention relates to the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the manufacture of a pharmaceutical composition for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, especially in the treatment of disorders or disease states in which the NPY-Y5 receptor subtype is involved, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes,

dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates to a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof as described hereinbefore and hereinafter for the prophylaxis and treatment of diseases or disorders associated with NPY Y5 receptor subtype, preferably, in the treatment of diseases caused by eating disorders, such as obesity, bulimia nervosa, diabetes, dyspilipidimia, and hypertension, furthermore in the treatment of memory loss, epileptic seizures, migraine, sleep disturbance, and pain, and additionally in the treatment of sexual/reproductive disorders, depression, anxiety, cerebral hemorrhage, shock, congestive heart failure, nasal congestion and diarrhea.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof, e.g. in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, halo-lower alkyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl, or (carbocyclic or heterocyclic) aryl-lower alkyl;

R_2 represents

(i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, or by substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) carbamoyl or N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-

substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

(vii) an element of formula $-X_3(X_4)(X_5)$ wherein, (a) if X_3 is -CH-, X_4 together with X_5 represent a structural element of formula $-X_6-(CO)_p-(CH_2)_o-$, $-(CH_2)_q-X_6-(CO)_p-(CH_2)_r-$, or $-(CH_2)_s-X_6-CO-(CH_2)_t-$; or, (b) if X_3 is -N-, X_4 together with X_5 represent a structural element of formula $-CO-(CH_2)_u-$; [X_6 being $-CH_2-$, $-N(R_1)-$ or -O-; the integer o is 3-5; the integer p is 0 or 1; the integer q is 1or 2; the integer r is 1; the integer s is 1 or 2; the integer t is 1 or 2; the integer u is 3-5; with the proviso that, if the integer p is 0, X_4 is different from $-CH_2-$;];

X_1 represents C_3-C_8-cycloalkylene, C_3-C_8-cycloalkenylene, C_3-C_8-cycloalkylidene, oxo-C_3-C_8-cycloalkylene, oxo-C_3-C_8-cycloalkenylene, or oxo-C_3-C_8-cycloalkylidene;

X_2 represents -O-, $-S(O)_n-$ or a group of the formula $-N(R_4)-$;

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and $-S(O)_n-R$;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, or by substituted carbamoyl;
(ii) amino or substituted amino;
(iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;
(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;
(v) N-substituted carbamoyl;
(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

X_1 represents C_3-C_8-cycloalkylene, C_3-C_8-cycloalkenylene, C_3-C_8-cycloalkylidene, oxo-C_3-C_8-cycloalkylene, oxo-C_3-C_8-cycloalkenylene, or oxo-C_3-C_8-cycloalkylidene;

X_2 represents -O-, -$S(O)_n$- or a group of the formula -N(R_4)-;

R_3 and R_4 , independently of one another, represent
(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or
(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, aroyl, or aryloxy, respectively, is derived and selected from the group consisting of phenyl, biphenylyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl, pyridyl, indolyl, indazolyl, benzofuryl, benzothiophenyl, benzimidazolyl, quinolinyl, isochinolyl, or quinazolinyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by $-CO-(O)_v-R$ and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(i) hydrogen, halogen, lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by substituted amino, by lower alkoxycarbonyl, by (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl, or by substituted carbamoyl;

(ii) amino or substituted amino;

(iii) hydroxy, lower alkoxy, lower alkenyloxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, C_3-C_8-cycloalkyl-lower alkoxy, (carbocyclic or heterocyclic) aryl-lower alkoxy, lower alkoxycarbonyl-oxy, (carbocyclic or heterocyclic) aryl-lower alkoxycarbonyl-oxy, or N-substituted aminocarbonyl-oxy;

(iv) lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, or (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(v) N-substituted carbamoyl;

(vi) a group selected from -CH(OH)-R, -CO-R, -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R, -NR_1-SO_2-NR_1-R, -SO_2-R, -SO_2-NR_1-R, or -SO_2-NR_1-CO-R, [R being as defined below and R_1 being as defined above, or the group -N(R)(R_1) represents amino which is di-substituted by lower alkylene {which may be interrupted by O, $S(O)_n$ or NR_0} or which is di-substituted by lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring]; or

X_1 represents C_3-C_8-cycloalkylene, C_3-C_8-cycloalkenylene, C_3-C_8-cycloalkylidene, oxo-C_3-C_8-cycloalkylene, oxo-C_3-C_8-cycloalkenylene, or oxo-C_3-C_8-cycloalkylidene;

X_2 represents -O-, -$S(O)_n$- or a group of the formula -N(R_4)-;

R_3 and R_4 , independently of one another, represent

(i) hydrogen, lower alkyl, lower alkenyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, (carbocyclic or heterocyclic) aryl-lower alkyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, amino,

substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, substituted carbamoyl, and -$S(O)_n$-R;

R_3 and R_4 together represent lower alkylene [which may be interrupted by O, $S(O)_n$, or NR_0] or represent lower alkylene which is condensed at two adjacent carbon atoms with a benzene ring;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

(i) halogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, (carbocyclic or heterocyclic) aryl, lower alkoxy, lower alkenyloxy, oxy-lower alkylene-oxy, hydroxy, lower alkanoyloxy, (carbocyclic or heterocyclic) aryl-lower alkanoyloxy, lower alkanoyl, (carbocyclic or heterocyclic) aryl-lower alkanoyl, nitro, cyano;

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, amino, substituted amino, carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iii) lower alkoxy which is substituted by a substituent selected from the group consisting of: halogen, hydroxy, lower alkoxy, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryloxy, amino, substituted amino, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl, carbamoyl, and N-substituted carbamoyl;

(iv) amino, substituted amino;

(v) carboxy, lower alkoxy-carbonyl, lower alkoxy-lower alkoxy-carbonyl, (carbocyclic or heterocyclic) aryl-lower alkoxy-carbonyl;

(vi) carbamoyl and N-substituted carbamoyl;

wherein, in each case, any aryl moiety, for example, of (carbocyclic or heterocyclic) aryl, arylene, aroyl, or aryloxy, respectively, is derived from phenyl, naphthyl or pyridyl;

wherein, in each case, the amino group of substituted amino, of N-substituted carbamoyl, and of N-substituted aminocarbonyl-oxy is (i) mono-substituted or, independently of one another, di-substituted by lower alkyl, by C_3-C_8-cycloalkyl, by C_3-C_8-cycloalkyl-lower alkyl, by (carbocyclic or heterocyclic) aryl, by (carbocyclic or heterocyclic) aryl-lower alkyl, or is (ii) di-substituted by lower alkylene [which may be interrupted by O, $S(O)_n$ or NR_0] or is di-substituted by lower alkylene which is condensed at two adjacent

carbon atoms with a benzene ring, or is (iii) mono-substituted or, in the second line, independently of one another, di-substituted by -CO-$(O)_v$-R and the integer v is 0 or 1;

wherein, in each case, the integer n is 0, 1 or 2;

wherein, in each case, R_0 represents hydrogen or lower alkyl;

wherein, in each case, R represents hydrogen, lower alkyl, C_3-C_8-cycloalkyl, (carbocyclic or heterocyclic) aryl-lower alkyl, (carbocyclic or heterocyclic) aryl, or lower alkyl which is substituted by halogen, by hydroxy, or by lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or lower alkylene;

R_1 represents hydrogen, lower alkyl, lower alkenyl, or lower alkoxy-lower alkyl;

R_2 represents

(i) hydrogen;

(ii) amino, amino which is monosubstituted by lower alkyl or phenyl-lower alkyl or is disubstituted by lower alkyl or by C_2-C_6-alkylene or amino which is monosubstituted by -CO-O-R and R being lower alkyl;

(iii) lower alkoxycarbonyl-oxy or (carbocyclic or heterocyclic) aryl-carbonyl-oxy;

(vi) a group selected from -CH(OH)-R and R being hydrogen, lower alkyl or phenyl-lower alkyl, -CO-R and R being hydrogen or lower alkyl, -NR_1-CO-O-R and R_1 being hydrogen and R being lower alkyl, -NR_1-CO-R and R_1 being hydrogen or lower alkyl and R being lower alkyl, phenyl or lower alkoxy-lower alkyl, -NR_1-SO_2-R and R_1 being hydrogen or lower alkyl and R being lower alkyl, phenyl-lower alkyl, phenyl or naphthyl, -NR_1-SO_2-NR_1-R and R_1 being hydrogen and -$N(R_1)(R)$ being amino disubstituted by lower alkyl or by C_2-C_6-alkylene or being morpholino, piperazino or 4-lower alkyl-piperazino, -SO_2-R and R being lower alkyl or phenyl;

X_1 represents C_3-C_8-cycloalkylene, especially cyclohexylene;

X_2 represents -O- and R_3 is hydrogen; or

X_2 represents a group of the formula -$N(R_4)$- and R_4 is hydrogen or lower alkyl; and

R_3 represents

(i) hydrogen, lower alkyl, C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-lower alkyl, or phenyl; or

(ii) lower alkyl which is substituted by a substituent selected from the group consisting of: hydroxy, lower alkoxy, hydroxy-lower alkoxy, amino, amino monosubstituted by lower

alkoxycarbonyl or disubstituted by lower alkyl, morpholino, piperazino, 4-lower alkyl-piperazino, 4-lower alkoxycarbonyl-piperazino and carbamoyl disubstituted by lower alkyl; or

X_2 and R_3 together represent morpholino or 4-lower alkyl-piperazino;

wherein, in each case, any aryl moiety as well as the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, nitro, lower alkyl, phenyl, hydroxy, lower alkoxy, hydroxy-lower alkoxy, lower alkoxycarbonyl-lower alkoxy and lower alkoxycarbonyl.

The invention relates especially to a compound of formula (I) or a salt or tautomer thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen or lower alkyl;

R_2 represents

hydrogen, lower alkoxycarbonyl-oxy, amino, amino disubstituted by C_3-C_6-alkylene, a group selected from -NR_1-CO-O-R [R being lower alkyl and R_1 being hydrogen], -NR_1-CO-R [R being lower alkyl, hydroxy-lower alkyl, phenyl-lower alkyl, or phenyl and R_1 being hydrogen], -NR_1-SO_2-R [R being lower alkyl, C_3-C_6-cycloalkyl, phenyl-lower alkyl, naphthyl-lower alkyl, phenyl, naphthyl, or quinolinyl and R_1 being hydrogen and the aryl radicals being unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxycarbonyl], -NR_1-SO_2-NR_1-R [R_1 being hydrogen, and the group-N(R)(R_1) being di-lower alkylamino, 1-piperidino, 1-piperazino, 4-lower alkyl-1-piperazino, or 4-morpholino] ,

-SO_2-R [R being lower alkyl], or -SO_2-NR_1-R, [R and R_1 being each lower alkyl];

X_1 represents C_3-C_6-cycloalkylene or C_3-C_6-cycloalkylidene;

X_2 represents O and R_3 represents hydrogen; or

X_2 represents a group of the formula -N(R_4)-; and

R_3 represents hydrogen, lower alkyl, lower alkyl substituted by hydroxy, lower alkoxy, hydroxy.lower alkoxy, di-lower alkylamino, or phenyl which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

R_4 represents hydrogen or lower alkyl;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of

halogen, lower alkyl, lower alkoxy, hydroxy-lower alkoxy, lower alkoxy-lower alkoxy, di-lower alkylamino, and phenyl-amino.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk_1 and alk_2, independently of one another, represent a single bond or C_1-C_3-alkylene;

R_1 represents hydrogen;

R_2 represents

hydrogen, lower alkoxycarbonyl-oxy, amino, amino di-substituted by C_3-C_6-alkylene, a group selected from -NR_1-CO-R [R being lower alkyl, phenyl-lower alkyl, or phenyl and R_1 being hydrogen], -NR_1-CO-O-R [R being lower alkyl], -NR_1-SO_2-R [R being lower alkyl, phenyl-lower alkyl, phenyl, naphthyl, or quinolinyl and R_1 being hydrogen and phenyl being unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkoxycarbonyl], -NR_1-SO_2-NR_1-R [R_1 being hydrogen, and the group-N(R)(R_1) being di-lower alkylamino] , -SO_2-R [R being lower alkyl], or -SO_2-NR_1-R, [R and R_1 being each lower alkyl];

X_1 represents C_3-C_6-cycloalkylene, especially 1,3-cyclopentylen, 1,3-, or 1,4-cycloalkylene;

X_2 represents O and R_3 represents hydrogen; or

X_2 represents a group of the formula -N(R_4)-; and

R_3 represents hydrogen, lower alkyl, or phenyl which is unsubstituted or substituted by halogen, lower alkyl, or lower alkoxy;

R_4 represents hydrogen;

wherein the benzo ring A is unsubstituted or substituted by one or more substituents selected from the group consisting of halogen or lower alkoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

alk_1 and alk_2 independently of one another, represent a single bond or methylene;

R_1 is hydrogen;

X_1 is 1,4-cyclohexylene;

X_2 is -O-; R_2 is -NH-SO_2-R and R being naphthyl; and R_3 is hydrogen; or

X_2 is -NH-;

R_2 represents -NH-SO_2-R and R is phenyl substituted by halogen, espechially 4-chloro-phenyl, or naphthyl; and R_3 represents hydrogen, C_1-C_4-alkyl which substituted by C_1-C_4-alkyl-amino or by C_1-C_4-alkyl-amino-carbonyl or by C_5-C_5-alkylene; or

R_2 represents C_1-C_4-alkylamino, such as methylamino, C_1-C_4-alkoxycarbonyl-amino, such as tert-butoxycarbonyl-amino, -NH-SO_2-R and R being phenyl substituted by C_1-C_4-alkyl, such as 4-methyl-phenyl, or C_1-C_4-alkyl, such as methyl, or is NH-SO_2-N(R_1)(R) and R_1 and R each being C_1-C_4-alkyl, such as methyl or ethyl; and R_3 represents hydrogen, phenyl or phenyl which is substituted by halogen, such as 4-fluoro- or 4-chloro-phenyl;
wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, such as methoxy.

The invention relates especially to a new compound of formula (I) or a salt or a tautomer thereof in which

X_1 represents 1,3- or 1,4-cyclohexylene;

X_2 represents a group of the formula -N(R_4)-;

R_1 represents hydrogen;

R_3 represents hydrogen;

R_4 represents hydrogen;

alk_1 and alk_2 each represent a single bond; and R_2 represents hydrogen; or

alk_1 represents methylene and alk_2 represents C_1-C_2-alkylene; and R_2 represents a group -NR_1-SO_2-R [R being naphthyl, especially 1- or 2-naphthyl];

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2 each represent methylene,

X_1 represents 1,4-cyclohexylene;

X_2 represents a group of the formula -NH-;

R_2 represents amino which is disubstituted by C_4-C_5-alkylene, such as 1-piperidino; and R_3 represents phenyl which is substituted by halogen, especially 4-chloro-phenyl; or

R_2 represents -NH-SO_2-R and R being naphthyl; and R_3 represents hydrogen, C_1-C_4-alkyl which is substituted by di- C_1-C_4-alkylamino or by 4-C_1-C_4-alkyl-piperazino, such as 4-methyl-piperazino;
wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially methoxy, preferably in position 8 of the quinazoline ring.

The invention relates especially to a new compound of formula (I) or a salt thereof in which

alk_1 and alk_2 each represent methylene,

X_1 represents 1,4-cyclohexylene;

X_2 represents a group of the formula $-N(R_4)-$;

R_1, R_3, and R_4 each represents hydrogen;

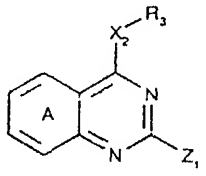
R_2 represents $-NH-SO_2-R$ and R represents 1- or 2-naphthyl; and

wherein the benzo ring A is unsubstituted or substituted by C_1-C_4-alkoxy, especially methoxy, in position 8 of the quinazoline ring.

The invention relates in particular to the novel compounds shown in the examples and to the modes of preparation described therein.

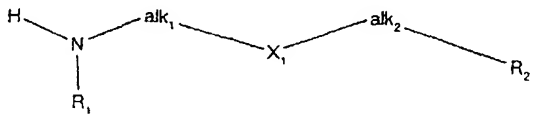
The invention relates to processes for the preparation of the compounds according to the invention. The preparation of new compounds of the formula (I) and their salts comprises, for example,

(a) reacting a compound of formula (IIa) or a salt thereof



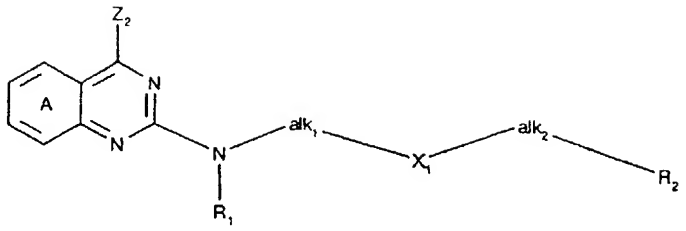
in which Z_1 represents a leaving group,

with a compound of formula (IIb) or a salt thereof



or

(b) reacting a compound of formula (IIIa) or a salt thereof



in which Z_2 is a leaving group

with a compound of formula H-X_2-R_3 (IIIb) or a salt thereof,

and, if desired, converting a compound (I) obtainable according to the process or in another manner, in free form or in salt form, into another compound (I), separating a mixture of isomers obtainable according to the process and isolating the desired isomer and/or converting a free compound (I) obtainable according to the process into a salt or converting a salt of a compound (I) obtainable according to the process into the free compound (I) or into another salt.

The reactions described above and below in the variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or a mixture thereof, the reaction, as required, being carried out with cooling, at room temperature or with warming, for example in a temperature range from about -80°C up to the boiling point of the reaction medium, preferably from about -10° to about +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. The person skilled in the pertinent art is especially referred to the methods as outlined in the working examples based upon which the person skilled in the art is enabled to carry out the manufacture of the compounds of formula (I).

Salts of starting materials which have at least one basic centre, for example of the formula IIIb, are appropriate acid addition salts, while salts of starting materials which have an acidic group, for example of the formula (IIb), are present as salts with bases, in each case as mentioned above in connection with corresponding salts of the formula (I).

A leaving group Z_1 or Z_2, respectively, is, for example, reactive esterified hydroxy, or is R'-S(O)$_u$- [the integer u being 0, 1 or 2 and R' being lower alkyl, halo-lower alkyl or aryl, such as methyl, trifluoromethyl or p-toluyl], or is lower alkoxy. Reactive esterified hydroxyl (Z_4) is in particular hydroxyl esterified with a strong inorganic acid or organic sulfonic acid, for example halogen, such as fluorine, chlorine, or bromine, sulfonyloxy, such as hydroxysulfonyloxy, halosulfonyloxy, for example fluorosulfonyloxy, C_1-C_7-alkane-sulfonyloxy which is unsubstituted or substituted, for example by halogen, for example methane- or trifluoromethanesulfonyloxy, C_5-C_7cycloalkanesulfonyloxy, for example cyclohexanesulfonyloxy, or benzenesulfonyloxy which is unsubstituted or substituted, for example by C_1-C_7alkyl or halogen, for example p-bromobenzene- or p-toluenesulfonyloxy. Preferred Z_1 or Z_2 is chloro, bromo or iodo, methanesulfonyloxy or trifluoromethanesulfonyloxy, or p-toluenesulfonyloxy, or methylthio or methoxy.

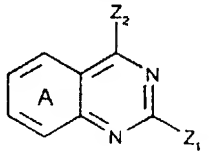
The reactions of process variants (a) and (b) are carried out, if necessary, in the presence of a base. Suitable bases are, for example, alkali metal hydroxides, hydrides, amides, alkanolates, carbonates, triphenylmethylides, di-lower alkylamides, aminoalkylamides or lower alkylsilylamides, naphthaleneamines, lower alkylamines, basic heterocycles, ammonium hydroxides, and carbocyclic amines. Examples which may be mentioned are sodium hydroxide, sodium hydride, sodium amide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium carbonate, lithium triphenylmethylide, lithium diisopropylamide, potassium 3-(aminopropyl)amide, potassium bis(trimethylsilyl)amide, dimethylaminonaphthalene, di- or triethylamine, or ethyldiisopropylamine, N-methylpiperidine, pyridine, benzyltrimethylammonium hydroxide, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU).

The starting material of fomulae (IIa), (IIb), (IIIa), and (IIIb) is essentially known or is accessible analogously to preparation processes known per se.

The starting material of the formula (IIa) is essentially described, for example, in US Patent No. 5,064,833.

The starting material of formula (IIb) in which R_2 represents N-acylated or N-alkylated amino, such as a group of formula -NR_1-CO-O-R, -NR_1-CO-R, -NR_1-CO-NR_1-R, -NR_1-SO_2-R,-NR_1-SO_2-NR_1-R, or N-substituted amino, is accessible, for example, by N-acylating or by N-alkylating, respectively, a, preferably N-protected, compound of the formula NH(R_1)-alk_1-X-alk_2-Z_3 (IIc) in which Z_3 represents a group which is convertable to R_2, such as amino, carboxy, or hydroxy. Conventional protecting groups may be used, for example, t-butoxycarbonyl which will be split off after the N-acylation or the N-alkylation, respectively. The starting material of formula (IIb) in which R_2 represents carbamoyl or N-substituted carbamoyl, or esterified carboxy, can be manufactured starting from a compound of formula (IIc) in which Z_3 represents carboxy. The esterification or amidation can be carried out in a manner known per se. Starting fom a compound of formula (IIc) in which Z_3 is hydroxy, corresponding etherified or esterified derivatives are accessible using etherification or esterifaction methods known in the art.

The starting material of formula (IIIa) is accessible, for example, by selectively converting the Z_2-group in position 4 into a group which is desactivated, for example, by selectively hydrolyzing a compound of formula (IIIc)



(IIa)

or a salt thereof to form a corresponding 4-hydroxy-compound (X_2 being O and R_3 being hydrogen) which is in the next step reacted with a compound of formula (IIb) to introduce the corresponding side chain into position 2 of the quinazoline ring. Reactivation of the 4-position, if required, for example, by reaction with a halogenating agent, such as $POCl_3$, leads to corresponding compounds of formula (IIIa) in which X_2 is N(R_4).

A compound according to the invention which is obtainable by the process can be converted into another compound according to the invention in a manner known per se.

A compound according to the invention containing hydroxyl can be etherified by methods known per se. The etherification can be carried out, for example, using an alcohol, such as a substituted or unsubstituted lower alkanol, or a reactive ester thereof. Suitable reactive esters of the desired alcohols are, for example, those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or substituted or unsubstituted benzenesulfonates, for example chlorides, bromides, iodides, methane-, benzene- or p-toluenesulfonates. The etherification can be carried out, for example, in the presence of a base, an alkali metal hydride, hydroxide or carbonate, or of an amine. Conversely, corresponding ethers, such as lower alkoxy compounds, can be cleaved, for example, by means of strong acids, such as mineral acids, for example the hydrohalic acids hydrobromic or hydriodic acid, which may advantageously be present in the form of pyridinium halides, or by means of Lewis acids, for example halides of elements of main group III or the corresponding sub-groups. These reactions can be carried out, if necessary, with cooling or warming, for example in a temperature range from about -20° to about 100°C, in the presence or absence of a solvent or diluent, under inert gas and/or under pressure and, if appropriate, in a closed vessel.

Compounds according to the invention containing hydroxymethyl groups can be prepared, for example, starting from compounds containing corresponding carboxyl or esterified carboxyl, corresponding compounds being reduced in a manner known per se, for example by reduction with a hydride which, if desired, may be complex, such as a hydride formed from an element of the 1st and 3rd main groups of the periodic table of the elements, for example borohydride or aluminohydride, for example lithium borohydride, lithium aluminium hydride, diisobutylaluminium hydride (an additional reduction step using alkali metal cyanoborohydride, such as sodium cyanoborohydride, may be necessary), and also diborane.

If an aromatic structural component is substituted by (lower) alkylthio (in $S(O)_n$ -R n is 0), this can be oxidised in a customary manner to corresponding (lower) alkanesulfinyl or -sulfonyl. Suitable oxidising agents for the oxidation to the sulfoxide step are, for example, inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulfuric acid, organic peracids, such as appropriate percarboxylic or persulfonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or p-toluenepersulfonic acid, or mixtures of hydrogen peroxide and acids, for example a mixture of hydrogen peroxide with acetic acid.

The oxidation is commonly carried out in the presence of suitable catalysts, catalysts which can be mentioned being suitable acids, such as substituted or unsubstituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of sub-group VII, for example vanadium oxide, molybdenum oxide or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures from about -50° to about +100°C.

The oxidation to the sulfone step may also be carried out appropriately at low temperatures using dinitrogen tetroxide as the catalyst in the presence of oxygen, just like the direct oxidation of (lower) alkylthio to (lower) alkanesulfonyl. However, in this case the oxidising agent is customarily employed in an excess.

If one of the variables contains amino, corresponding compounds of the formula (I), their tautomers or salts can be N-alkylated in a manner known per se; likewise, carbamoyl or radicals containing carbamoyl can be N-alkylated. The (aryl)alkylation is carried out, for example, using a reactive ester of an (aryl)C_1-C_7alkyl halide, for example a bromide or iodide, (aryl)C_1-C_7alkylsulfonate, for example methanesulfonate or p-toluenesulfonate, or a di-C_1-C_7alkyl sulfate, for example dimethyl sulfate, preferably under basic conditions, such as in the presence of sodium hydroxide solution or potassium hydroxide solution, and advantageously in the presence of a phase transfer catalyst, such as tetrabutylammonium bromide or benzyltrimethylammonium chloride, where,

however, stronger basic condensing agents, such as alkali metal amides, hydrides or alkoxides, for example sodium amide, sodium hydride or sodium ethoxide, may be necessary. Amino can also be acylated in a manner known per se.

In compounds of the formula (I) which contain an esterified or amidated carboxyl group as a substituent, a group of this type can be converted into a free carboxyl group, for example by means of hydrolysis, for example in the presence of a basic agent, or of an acidic agent, such as a mineral acid. Tert-butyloxycarbonyl, for example, can furthermore be converted into carboxyl, for example in a manner known per se, such as treating with trihaloacetic acid, such as trifluoroacetic acid, and benzyloxycarbonyl can be converted into carboxyl, for example by catalytic hydrogenation in the presence of a hydrogenation catalyst, for example in the manner described below.

Furthermore, in compounds of the formula (I) which contain a carboxyl group as a substituent, this can be converted into an esterified carboxyl group, for example, by treating with an alcohol, such as a lower alkanol, in the presence of a suitable esterifying agent, such as an acid reagent, for example an inorganic or organic acid or a Lewis acid, for example zinc chloride, or a condensing agent which binds water, for example a carbodiimide, such as N,N'-dicyclohexylcarbodiimide, or by treating with a diazo reagent, such as with a diazo-lower alkane, for example diazomethane. This can also be obtained if compounds of the formula (I) in which the carboxyl group is present in free form or in salt form, such as ammonium salt or metal salt form, for example alkali metal salt form, such as sodium salt or potassium salt form, are treated with a reactive ester of a (C_1-C_7)alkyl halide, for example methyl or ethyl bromide or iodide, or an organic sulfonic acid ester, such as an appropriate (C_1-C_7)alkyl ester, for example methyl or ethyl methanesulfonate or p-toluenesulfonate.

Compounds of the formula (I) which contain an esterified carboxyl group as a substituent can be transesterified into other ester compounds of the formula (I) by transesterification, for example by treating with an alcohol, customarily a higher appropriate alcohol than that of the esterified carboxyl group in the starting

material, in the presence of a suitable transesterifying agent, such as a basic agent, for example an alkali metal (C_1-C_7)alkanoate, (C_1-C_7)alkanolate or alkali metal cyanide, such as sodium acetate, sodium methoxide, sodium ethoxide, sodium tert-butoxide or sodium cyanide, or a suitable acid agent, if appropriate with removal of the resulting alcohol, for example by distillation. Appropriate, so-called activated esters of the formula (I) which contain an activated esterified carboxyl group as a substituent may also be used as starting materials (see below), and these may be converted into another ester by treating with a (C_1-C_7)alkanol.

In compounds of the formula (I) which contain the carboxyl group as a substituent, this can also first be converted into a reactive derivative, such as an anhydride, including a mixed anhydride, such as an acid halide, for example an acid chloride (for example by treating with a thionyl halide, for example thionyl chloride), or an anhydride using a formic acid ester, for example a (C_1-C_7)alkyl ester (for example by treating a salt, such as an ammonium or alkali metal salt, with a haloformic acid ester, such as a chloroformic acid ester, such as a (C_1-C_7)alkyl ester), or into an activated ester, such as a cyanomethyl ester, a nitrophenyl ester, for example a 4-nitrophenyl ester, or a polyhalophenyl ester, for example a pentachlorophenyl ester (for example by treating with an appropriate hydroxyl compound in the presence of a suitable condensing agent, such as N,N'-dicyclohexylcarbodiimide), and then a reactive derivative of this type can be reacted with an amine and in this way amide compounds of the formula (I) which contain an amidated carboxyl group as a substituent can be obtained. In this case, these can be obtained directly or via intermediate compounds; thus, for example, an activated ester, such as a 4-nitrophenyl ester, of a compound of the formula (I) containing a carboxyl group can first be reacted with a 1-unsubstituted imidazole and the 1-imidazolylcarbonyl compound obtained in this way brought to reaction with an amine. However, other non-activated esters, such as (C_1-C_7)alkyl esters of compounds of the formula (I), which contain, for example, (C_2-C_8)alkoxycarbonyl as a substituent, can also be brought to reaction with amines.

If an aromatic ring contains a hydrogen atom as a substituent, the latter can be replaced by a halogen atom with the aid of a halogenating agent in a customary

manner, for example brominated with bromine, hypobromic acid, acyl hypobromites or other organic bromine compounds, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxane dibromide, 1,3-dibromo-5,5-dimethylhydantoin or 2,4,4,6-tetrabromo-2,5-cyclohexanedien-1-one, or chlorinated with elemental chlorine, for example in a halogenated hydrocarbon, such as chloroform, and with cooling, for example from down to about -10° to about +100°C.

If an aromatic ring in the compounds according to the invention contains an amino group, this can be diazotized in a customary manner, for example by treating with a nitrite, for example sodium nitrite, in the presence of a suitable protonic acid, for example a mineral acid, the reaction temperature advantageously being kept below about 5°C. The diazonium group present in the salt form and obtainable in this way can be substituted by analogous processes, for example as follows: by the hydroxyl group analogously to the boiling-out of phenol in the presence of water; by an alkoxy group by treating with an appropriate alcohol, energy having to be added; by the fluorine atom analogously to the Schiemann reaction in the thermolysis of corresponding diazonium tetrafluoroborates; by the halogen atoms chlorine, bromine or iodine and also the cyano group analogously to the Sandmeyer reaction in the reaction with corresponding Cu(I) salts, initially with cooling, for example to below about 5°C, and then heating, for example to about 60° to about 150°C.

If the compounds of the formula (I) contain unsaturated radicals, such as (lower) alkenyl or (lower) alkynyl groups, these can be converted into saturated radicals in a manner known per se. Thus, for example, multiple bonds are hydrogenated by catalytic hydrogenation in the presence of hydrogenation catalysts, suitable catalysts for this purpose being, for example, nickel, such as Raney nickel, and noble metals or their derivatives, for example oxides, such as palladium or platinum oxide, which may be applied, if desired, to support materials, for example to carbon or calcium carbonate. The hydrogenation may preferably be carried out at pressures between 1 and about 100 at and at room temperature between about -80° to about 200°C, in particular between room temperature and about 100°C. The reaction is advantageously carried out in a solvent, such as

water, a lower alkanol, for example ethanol, isopropanol or n-butanol, an ether, for example dioxane, or a lower alkanecarboxylic acid, for example acetic acid.

Furthermore, in compounds of the formula (I) in which, for example, one of the aryl radicals contains halogen, such as chlorine, halogen can be replaced by reaction with a substituted or unsubstituted amine, an alcohol or a mercaptan.

The invention relates in particular to the processes described in the examples.

Salts of compounds of the formula (I) can be prepared in a manner known per se. Thus, for example, acid addition salts of compounds of the formula (I) are obtained by treating with an acid or a suitable ion exchange reagent. Salts can be converted into the free compounds in a customary manner, and acid addition salts can be converted, for example, by treating with a suitable basic agent.

Depending on the procedure and reaction conditions, the compounds according to the invention having salt-forming, in particular basic properties, can be obtained in free form or preferably in the form of salts.

In view of the close relationship between the novel compound in the free form and in the form of its salts, in the preceding text and below the free compound or its salts may correspondingly and advantageously also be understood as meaning the corresponding salts or the free compound.

The novel compounds including their salts of salt-forming compounds can also be obtained in the form of their hydrates or can include other solvents used for crystallization.

Depending on the choice of the starting materials and procedures, the novel compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, such as antipodes, or as isomer mixtures, such as racemates, diastereoisomer mixtures or racemate mixtures, depending on the number of asymmetric carbon atoms. For example, compounds of the formula (I) in which e.g. X_1 has an asymmetric C atom.

Racemates and diastereomer mixtures obtained can be separated into the pure isomers or racemates in a known manner on the basis of the physicochemical differences of the components, for example by fractional crystallization. Racemates obtained may furthermore be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilized enzymes, via the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereomeric salts, for example by reaction of a basic final substance racemate with an optically active acid, such as a carboxylic acid, for example tartaric or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the diastereomer mixture obtained in this manner, for example on the basis of its differing solubilities, into the diastereomers from which the desired enantiomer can be liberated by the action of suitable agents. The more active enantiomer is advantageously isolated.

The invention also relates to those embodiments of the process, according to which a compound obtainable as an intermediate in any step of the process is used as a starting material and the missing steps are carried out or a starting material in the form of a derivative or salt and/or its racemates or antipodes is used or, in particular, formed under the reaction conditions.

In the process of the present invention, those starting materials are preferably used which lead to the compounds described as particularly useful at the beginning. The invention likewise relates to novel starting materials which have been specifically developed for the preparation of the compounds according to the invention, to their use and to processes for their preparation, the variables alk_1, alk_2, R_1, R_2, R_3, R_4, X_1 and X_2 having the meanings indicated for the preferred compound groups of the formula (I) in each case.

The invention likewise relates to pharmaceutical preparations which contain the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for their preparation.

The pharmaceutical preparations according to the invention which contain the compound according to the invention or pharmaceutically acceptable salts thereof are those for enteral, such as oral, furthermore rectal, and parenteral administration to (a) warm-blooded animal(s), the pharmacological active ingredient being present on its own or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends on the age and the individual condition and also on the manner of administration.

The novel pharmaceutical preparations contain, for example, from about 10 % to about 80%, preferably from about 20 % to about 60 %, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as sugar-coated tablets, tablets, capsules or suppositories, and furthermore ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, if desired granulating a mixture obtained, and processing the mixture or granules, if desired or necessary, after addition of suitable excipients to give tablets or sugar-coated tablet cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, furthermore binders, such as starch paste, using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired, disintegrants, such as the abovementioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate; auxiliaries are primarily glidants, flow-regulators and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Sugar-coated tablet cores are provided with suitable coatings which, if desired, are resistant to gastric juice, using, inter alia, concentrated sugar solutions which, if desired, contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide,

coating solutions in suitable organic solvents or solvent mixtures or, for the preparation of gastric juice-resistant coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colorants or pigments, for example to identify or to indicate different doses of active ingredient, may be added to the tablets or sugar-coated tablet coatings.

Other orally utilizable pharmaceutical preparations are hard gelatin capsules, and also soft closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The hard gelatin capsules may contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Suitable rectally utilizable pharmaceutical preparations are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. Furthermore, gelatin rectal capsules which contain a combination of the active ingredient with a base substance may also be used. Suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparations for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and furthermore suspensions of the active ingredient, such as appropriate oily injection suspensions, using suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if necessary, also stabilizers.

The dose of the active ingredient depends on the warm-blooded animal species, the age and the individual condition and on the manner of administration. In the normal case, an approximate daily dose of about 10 mg to about 250 mg is to be estimated in the case of oral administration for a patient weighing approximately 75 kg .

The following examples illustrate the invention described above; however, they are not intended to limit its extent in any manner. Temperatures are indicated in degrees Celsius.

The following examples illustrate the invention.

Abbreviations:

HCl	hydrochloric acid
NaOH	sodium hydroxide
THF	tetrahydrofuran
min	minute(s)
h	hour(s)
m.p.	melting point
FAB-MS	Fast Atom Bombardment Mass Spectroscopy
ESI-MS	Electro-Spray Inonization Mass Spectroscopy
Rf	retention factor on a thin layer chromatography plate

Solvent systems (v/v/v):

A1:	hexanes / ethyl acetate	1:1
A2:	hexanes / ethyl acetate	19:1
A3:	hexanes / ethyl acetate	4:1
A4:	hexanes / ethyl acetate	2:1
A5:	hexanes / ethyl acetate	3:1
A6:	ethyl acetate	
A7:	toluene / ethyl acetate	1:1
A8:	hexanes / ethyl acetate	1:2
A9:	hexanes / ethyl acetate / dichloromethane	12:6:1

A10:	hexanes / ethyl acetate / dichloromethane	8:8:1
A11:	hexanes / ethyl acetate	10:1
B1:	dichloromethane / methanol	19:1
B2:	dichloromethane / methanol	9:1
B3:	dichloromethane / methanol	5:1
B4:	dichloromethane / methanol	4:1
B5:	dichloromethane / methanol	1:1
B6:	dichloromethane / methanol	85:15
B7:	dichloromethane / methanol	7:1
B8:	dichloromethane / methanol	7:3
B9:	dichloromethane / methanol	97:3
B10:	dichloromethane	
C1:	dichloromethane / methanol / ammonium hydroxide	95: 5:0.5
C2:	dichloromethane / methanol / ammonium hydroxide	90:10:1
C3:	dichloromethane / methanol / ammonium hydroxide	80:20:2
C4:	dichloromethane / methanol / ammonium hydroxide	98:2:0.2
C5:	dichloromethane / methanol / ammonium hydroxide	350:50:1
C6:	dichloromethane / methanol / ammonium hydroxide	96:4:0.4
C7:	dichloromethane / methanol / ammonium hydroxide	70:30:3
C8:	dichloromethane / methanol / ammonium hydroxide	60:4:1
C9:	dichloromethane / methanol / ammonium hydroxide	20:4:1
C10:	dichloromethane / methanol / ammonium hydroxide	40:4:1
D1:	dichloromethane / methanol / water / acetic acid	170:26:3:1
D2:	dichloromethane / methanol / water / acetic acid	150:54:10:1
E1:	ethyl acetate / ethanol / ammonium hydroxide	6:3:1
E2:	ethyl acetate / methanol / ammonium hydroxide	40:10:1
F1:	toluene / isopropanol / acetic acid	85:15:1
G1:	toluene / ethanol / chloroform / ammonium hydroxide	85:15:1

Example 1: 2-Cyclohexylamino-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (1.2 g) and cyclohexylamine (0.69 ml) is heated to for 4 min to produce a melt which is dissolved in isopropanol (15 ml). 4 N HCl in dioxane (0.2 ml) is added and the solvents are removed in vacuo. The residue is

recrystallized from isopropanol and diethylether to give 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride; m.p. 236 - 238°C, Rf(F1) 0.13.

The starting material can be prepared, for example, as follows:

a) 2-Chloro-4-phenylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (15 g), N,N-diisopropyl-ethylamine (24.9 ml) and aniline (7.5 ml) in isopropanol (75 ml) is heated to reflux for 45 min. The cold reaction mixture is filtered and the filtrate is concentrated in vacuo. The residue is crystallized from diethylether- toluene (1:1) to give 2-chloro-4-phenylamino-quinazoline, m.p. 194 - 196°C.

b) 2,4-Dichloro-quinazoline

N,N-Dimethylaniline (114.0 g) is added slowly to a solution of 1H,3H-quinazolin-2,4-dione (146.0 g) in phosphorousoxychloride (535.4 ml) while this mixture is heated up to 140°C. After completion of the addition reflux is continued for 20 h . The reaction mixture is filtered and concentrated to give a residue which is added to ice and water. The product is extracted with dichloromethane and crystallized from diethylether and petroleum ether to yield 2,4-dichloro-quinazoline, m.p. 115 - 116°C.

Example 2: cis/trans-2-(4-Piperidin-1-yl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (0.76 g) and N-(4-amino-cyclohexyl)-piperidine (*J. Amer. Chem. Soc.* **1946**, *68*, 1296) (0.6 g) is heated for 3 min to produce a melt which is dissolved in isopropanol (10 ml). 4 N HCl in dioxane (1.0 ml) is added and the solvents are removed in vacuo. The residue is chromatographed on silica gel by eluting with ethyl acetate / methanol / ammonia (8:2:1) to give the free base which, dissolved in ethanol and treated with an excess of 4 N HCl in dioxane, yields cis/trans-2-(4-piperid-1-yl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride, Rf (E1) 0.13.

Example 3: 2-Cyclohexylamino-8-methoxy-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-8-methoxy-4-phenylamino-quinazoline (0.285 g) and cyclohexylamine (0.15 ml) is heated for 2 min to produce a melt which is dissolved in isopropanol. 4 N HCl in

dioxane (0.1 ml) is added. Crystallization from isopropanol and diethylether yields 2-cyclohexylamino-8-methoxy-4-phenylamino-quinazoline hydrochloride, m.p. 195 - 197°C.

The starting material can be prepared, for example, as follows:

2-Chloro-8-methoxy-4-phenylamino-quinazoline

A solution of 2,4-dichloro-8-methoxy-quinazoline (prepared as described in *J. Chem. Soc.* **1948**, 1759) (0.6 g), diisopropylethylamine (0.87 ml), and aniline (0.26 ml) in isopropanol (10 ml) is heated at reflux for 45 min. The cold reaction mixture is filtered and residue is crystallized from dichloromethane and hexanes to give 2-chloro-8-methoxy-4-phenylamino-quinazoline, m.p. 245 - 246°C.

Example 4: trans-2-(4-Acetoxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

A solution of trans-2-(4-hydroxy-cyclohexyamino)-4-phenylamino-quinazoline hydrochloride (1.3 g) and acetic anhydride (0.33 ml) in acetic acid (5 ml) is stirred at ambient temperature for 16 h. The solvent is removed in vacuo and the residue is added to 2N aqueous NaOH. Extraction with ethyl acetate followed by chromatography on silica gel (A4) gives a crude product which is treated with 4 N HCl in dioxane. Crystallization from acetonitrile and acetone yields trans-2-(4-acetoxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride, m.p. 217 - 220°C.

The starting material can be prepared, for example, as follows:

2-(4-Hydroxy-cyclohexyamino)-4-phenylamino-quinazoline hydrochloride

A mixture of 2-chloro-4-phenylamino-quinazoline (2.3 g) and trans-4-amino-cyclohexanol (1.26 g) is heated for 3 min to produce a melt which is dissolved in isopropanol. 4 N HCl in dioxane (0.1 ml) is added. Crystallization from isopropanol and acetone yields 2-(4-hydroxy-cyclohexyamino)-4-phenylamino-quinazoline hydrochloride, m.p. 258 - 259°C.

Example 5: trans-Naphthalene-1-sulfonic acid [4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (Example 1a) (0.256 g) and trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide (0.364 g) in iso-propanol (5 ml) is stirred at 120 °C for 17 h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is recrystallized from 1-octanol to give trans-naphthalene-1-sulfonic acid [4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride as colorless crystals melting at 174-176 °C; Rf(B2) 0.32, FAB-MS: $(M+H)^+$ = 537.

The starting material can be prepared, for example, as follows:

a) trans-4-[(1-Naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid
To a stirred solution of trans-4-(aminomethyl)-cyclohexanecarboxylic acid (60 g) in 1 N NaOH (917 ml) is added 1-naphthalenesulfonyl chloride (86.59 g) over 30 min at room temperature. The mixture is stirred at room temperature for 20 h. To the mixture is added 140 ml of 4 N HCl and 1 l of water, and the white crystals are collected by filtration to yield trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid as a white powder melting at 164 - 165 °C; Rf(A1) 0.16, FAB-MS: $(M+H)^+$ = 348.

b) trans-4-[(1-Naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide
To a stirred solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexane-carboxylic acid (100 g) and triethylamine (41.8 ml) in THF (500 ml) is added a solution of ethyl chloroformate (28.6 ml) in THF (30 ml) below 0 °C over 25 min. After stirring at 0 °C for 45 min, 25% aqueous ammonia solution (500 ml) is added to the above mixture at 0 - 5 °C over 10 min. The resulting mixture is stirred at room temperature for 90 min. To the mixture is added 2 l of water and the white solid is collected by filtration to give trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid amide as a white powder melting at 170 - 171 °C; Rf(C5) 0.40, FAB-MS: $(M+H)^+$ = 347.

c) trans-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide
To a stirred suspension of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexane-carboxylic acid amide (61.4 g) in THF (500 ml) is added a solution of diborane-THF complex in THF (1 M, 443 ml) below 28 °C over 50 min. The mixture is slowly warmed up and heated up to reflux for 2 h. After cooling to 0 °C, the reaction is quenched by adding 120 ml of water and 500 ml of 4 N HCl. To the mixture is added 1 l of methanol and the mixture is

concentrated under reduced pressure. The residue is treated with 1 l of methanol and concentrated under reduced pressure. The crude product is obtained as its HCl salt and is purified by recystallization from isopropanol (mp. 259 °C). To the purified HCl salt is added 1.2 l of 1 N NaOH and the resulting solution is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and concentrated under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide as a colorless amorphous solid; Rf(C5) 0.07.

d) trans-Naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amide

To a stirred solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexane-carboxylic acid (3 g) and triethylamine (1.45 ml) in THF (30 ml) is added dropwise to a solution of ethyl chloroformate (0.81 ml) in THF (4 ml) between -10 and -5 °C. After stirring at -10 °C for 20 min, a solution of sodium azide (1.12 g) in water (3.5 ml) is added to the mixture over 5 min. The resulting mixture is stirred for 30 min and is poured into 60 ml of ice-water. The mixture is extracted with toluene. After drying over sodium sulfate, the combined extracts are heated at reflux for 1h. The solvent is removed under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amid as a colorless oil; Rf(A1) 0.73.

e) trans-Naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide

A suspension of trans-naphthalene-1-sulfonic acid (4-isocyano-cyclohexylmethyl)-amide (1.3 g) in 20 ml of 4 N HCl is heated at reflux over night. The white solid is isolated by filtration and is washed with water. To the solid is added 15 ml of 1 N aqueous NaOH and the mixture is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and concentrated under reduced pressure to give trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide as a white powder melting at 137 - 138 °C; Rf(C5) 0.1, FAB-MS: $(M+H)^+$ = 319.

Example 6: trans-Naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-yl-amino)-cyclohexylmethyl]-amide hydrochloride

A suspension of 2-chloro-quinazolin-4-ylamine (see: US 3,956,495) (0.118 g) and trans-naphthalene-1-sulfonic acid (4-amino-cyclohexylmethyl)-amide (0.21 g) in 5 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and

chromatographed (silica gel, B2) to give the product as a foam. This material is taken up in dichloromethane and treated at 0 °C with a 4 N HCl solution in dioxane (0.2 ml). Concentration in vacuo provides a foam which is triturated in boiling cyclohexane to yield after filtration trans-naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-yl-amino)-cyclohexylmethyl]-amide hydrochloride, melting at 115 - 125 °C. Rf(B2) 0.24; FAB-MS: $(M+H)^+$ = 462.

Example 7: trans-[4-(4-Phenylamino-quinazoline-2-ylamino)-cyclohexylmethyl]-carbamic acid tert-butyl ester hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (9.72 g) and trans-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester (10.1 g) in isopentylalcohol (150 ml) is stirred at 120 °C for 20 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from isopropanol yields naphthalene-1-sulfonic acid trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride as a colorless crystals melting at 161 - 163 °C; Rf(D1) 0.44.

The starting material can be prepared, for example, as follows:

a) [4-(tert.-Butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester
To a stirred suspension of 4-(tert.-butoxycarbonylaminomethyl)-cyclohexanecarboxylic acid (obtained according to: FR 2,701,480) (45 g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) is added triethylamine (32 ml) below 0 °C over a period of 20 min. The mixture is slowly warmed up and stirred at 70 °C for 4 h. After cooling to 40 °C, benzyl alcohol (36 ml) is added and the reaction mixture is heated at reflux for 20 h. The cold reaction mixture is washed with water and brine and dried over magnesium sulfate. Concentration in vacuo followed by crystallisation from ethyl acetate and diethylether yields [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester as colorless crystals, melting at 126 - 129 °C. Rf(A7) 0.47.

b) trans-(4-Amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester
A solution of [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester (4 g) in methanol (200 ml) is hydrogenated in the presence of palladium on charcoal 10% (0.7 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate

is concentrated in vacuo to yield and trans-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester as a colorless oil, Rf(D1) 0.12.

Example 8: trans-4-(Aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A suspension of trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-amide hydrochloride (6.8 g) in chloroform (50 ml) is treated with a 4 N HCl solution in dioxane (20 ml) at 0 °C. After completion, the reaction mixture is concentrated in vacuo and the residue is recrystallized from isopropanol to yield trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride as white crystals melting at 326 - 330°C. The dihydrochloride salt is taken up in a saturated aqueous potassium carbonate solution and dichloromethane. After extraction with ethyl acetate, the organics are dried over sodium sulfate and concentrated to give trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline as a light yellow oil. Rf(G1) 0.04. FAB-MS: $(M+H)^+ = 348$.

Example 9: trans-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride

A solution of trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline (0.70 g) and diisopropylethylamine (0.41 ml) in dichloromethane (10 ml) or is cooled to 0 °C and treated with methanenesulfonylchloride (0.16 ml) in dichloromethane (2 ml). After completion, the reaction mixture is concentrated and the residue is taken up in water and extracted with ethyl acetate. The combined extracts are washed with brine, dried over magnesium sulfate and concentrated. The residue is dissolved in methanol and treated with a 4 N HCl in dioxane (0.5 ml). Concentration in vacuo followed by crystallization from isopropanol yields trans-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride melting at 240-245 °C. Rf(G1) 0.45.

Example 10: trans-4-Methyl-N-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-benzenesulfonamide hydrochloride

Reaction of trans-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline (0.79 g) with toluenesulfonylchloride (0.38 g) as described in Example 9 provides trans-4-methyl-N-

[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-benzenesulfonamide hydrochloride melting at 163-165 °C. Rf(G1) 0.53.

Example 11: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methoxy-benzenesulfonamide hydrochloride

A solution of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) and diisopropylethylamine (0.716 ml) in 4 ml of N,N-dimethyl-formamide is cooled to 0 °C and treated with 4-methoxybenzenesulfonylchloride (0.242 g) in N,N-dimethylformamide (2 ml). After completion, the reaction mixture is concentrated and the residue is chromatographed (silica gel, C1) to give the product as a foam. It is taken up in dichloromethane (2 ml) and treated at 0 °C with a 4 N HCl in dioxane (2 ml). Concentration in vacuo followed by crystallization from acetonitrile yields trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methoxy-benzenesulfonamide hydrochloride as a tan powder melting at 118 - 125 °C . Rf(C1) 0.38; FAB-MS: $(M+H)^+$ = 456.

The starting material can be prepared, for example, as follows:

a) trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester
A solution of trans-4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (obtained according to: EP 0614 911 A1) (34.5 g) and triethylamine (28 ml) in dichloromethane (700 ml) is cooled to -70 °C and treated with methylchloroformate (12.9 ml). The reaction mixture is stirred 0.5 h at -70°C . The temperature is allowed to increase to 0 °C and the solution is stirred another 0.5 h until completion of the reaction. The reaction mixture is taken up in ice-cold dichloromethane, washed with an ice-cold 0.5 N HCl solution, a saturated aqueous sodium carbonate solution and water. The organics are dried over sodium sulfate and concentrated to the mixted-anhydride as an oil. This material is taken up in THF and treated at - 70 °C with sodium borohydride (5.90 g), followed by absolute methanol (10 ml). The reaction mixture is stirred 15 h at 0 °C and 1 h at ambient temperature to drive the reaction to completion. A 0.5 N HCl solution is then carefuly added at 0°C, followed by ethyl acetate. The organics are washed with a saturated aqueous sodium carbonate solution, water, dried over sodium sulfate and concentrated.

Chromatography on silica gel (A1) yields trans-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as a white powder, melting at 88 - 89°C. Rf(A1) 0.24.

b) trans-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in pyridine (200 ml) at 0 °C is treated with a solution of para-toluenesulfonylchloride (24.44 g) in pyridine (50 ml). The reaction mixture is stirred at 0 °Cuntil completion and concentrated in vacuo. The residue is taken up in ethyl acetate, washed with water and dried over sodium sulfate. Concentration of the solution yields the tosylate, used without further purification. This material is treated with sodium azide (19.23 g) in N,N-dimethylformamide (800 ml) at 50°C. After completion of the reaction, the solution is concentrated and the resulting paste is taken up in dichloromethane, washed with water and concentrated. Chromatography of the crude material on silica gel (A2 then A3) provides trans-(4-azidomethyl-cyclohexyl-methyl)-carbamic acid tert-butyl ester as an oil. Rf(A3) 0.33; IR (dichloromethane) μ max 2099 cm^{-1}.

c) trans-(4-Aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

trans-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in ethyl acetate (1 liter) is hydrogenated over platinumoxide (2.4 g) at ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered-off and the filtrate concentrated to yield trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.41.

d) trans-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

A suspention of 5.0 g of 2-chloro-quinazolin-4-ylamine and 6.75 g of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester in 120 ml of isopentylalcohol is heated up to 120 °C for 15 h. The reaction mixture is concentrated and chromatographed on silica gel (B1 then B2) to give trans-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a foam. Rf(B2) 0.33.

e) trans-N-2-(4-Aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride

A solution of trans-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (9.58 g) in 130 ml of dichloromethane is cooled to 0 °C and treated with

130 ml of a 4 N HCl solution in dioxane. After completion, the reaction mixture is concentrated in vacuo to yield trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride melting at 189 - 192°C. Rf(C3) 0.54.

Example 12: trans-3-{{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-sulfamoyl}-4-methoxy-benzoic acid methyl ester hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with 2-methoxy-5-(methoxycarbonyl)-sulfonylchloride (0.332 g) as described in Example 11 provides trans-3-{{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-sulfamoyl}-4-methoxy-benzoic acid methyl ester hydrochloride melting at 140 - 150°C. Rf(C1) 0.28; FAB-MS: $(M+H)^+ = 514$.

The starting material can be prepared, for example, as follows:

a) 2-Methoxy-5-(methoxycarbonyl)-sulfonic acid

A solution of methyl 4-methoxybenzoate (50 g) in dichloromethane (800 ml) is cooled to 0 °C, treated by slow addition of chlorosulfonic acid (22.10 ml) and heated up to reflux for 12 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from diethylether yields 2-methoxy-5-(methoxycarbonyl)-sulfonic acid melting at 159 - 160°C.

b) 3-Chlorosufonyl-4-methoxy-benzoic acid methyl ester

A solution of 2-methoxy-5-(methoxycarbonyl)-sulfonic acid (55 g) in N,N-dimethylformamide (1 liter) is treated at 0 °Cwith pyridine (53.6 ml), followed by phosphorusoxychloride (61.5 ml) and stirred at ambient temperature for 15 h. The reaction mixture is taken up in diethylether and washed with ice-cold water. The organics are concentrated to ca. 150 ml and the product is allowed to crystallize out overnight. It is collected by suction filtration, triturated in hexanes and dried to give chlorosufonyl-4-methoxy-benzoic acid methyl ester, melting at 124 - 126 °C.

Example 13: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,5-dimethoxy-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with 2,5-dimethoxy-benzenesulfonylchloride (0.258 g) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,5-dimethoxy-benzenesulfonamide hydrochloride melting at 137 - 145°C. Rf(C1) 0.20; FAB-MS: $(M+H)^+$ = 486.

Example 14: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with benzenesulfonylchloride (0.161 ml) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzenesulfonamide hydrochloride melting at 111 - 123 °C. Rf(B2) 0.23; FAB-MS: $(M+H)^+$ = 426.

Example 15: trans-Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.2 g) with naphthalene-2-sulfonylchloride (0.127 mg) as described in Example 11 provides trans-naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-yl-amino)methyl]-cyclohexylmethyl}-amide hydrochloride melting at 105 - 120 °C. Rf(C2) 0.63; FAB-MS: $(M+H)^+$ = 476.

Example 16: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methanesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with methanesulfonylchloride (0.121 ml) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methanesulfonamide hydrochloride melting at 130 - 140°C. Rf(C2) 0.35; FAB-MS: $(M+H)^+$ = 364.

Example 17: trans-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-phenylmethanesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.3 g) with phenylmethanesulfonylchloride (0.223 g) as described in Example 11 provides trans-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-phenylmethanesulfonamide hydrochloride melting at 144 - 150 °C. Rf(C1) 0.32; FAB-MS: $(M+H)^+$ = 440.

Example 18: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-tert-butyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.26 g) with 4-tert-butyl-benzenesulfonylchloride (0.253 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-tert-butyl-benzenesulfonamide hydrochloride melting at 135 - 150°C. Rf(C2) 0.38; FAB-MS: $(M+H)^+$ = 482.

Example 19: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,4,6-trimethyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.27 g) with 2,4,6-trimethylbenzenesulfonylchloride (0.24 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2,4,6-trimethyl-benzenesulfonamide hydrochloride melting at 148 - 158 °C. Rf(C2) 0.35; FAB-MS: $(M+H)^+$ = 468.

Example 20: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methyl-benzenesulfonamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.38 g) with para-toluenesulfonylchloride (0.303 g) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-methyl-

benzenesulfonamide hydrochloride melting at 100 - 112 °C. Rf(C2) 0.53; FAB-MS: $(M+H)^+$ = 440.

Example 21: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with benzoylchloride (0.129 ml) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-benzamide hydrochloride melting at 150 - 160 °C. Rf(C2) 0.45; FAB-MS: $(M+H)^+$ = 390.

Example 22: trans-N-{4-[4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-phenyl-acetamide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with phenylacetylchloride (0.148 ml) as described in Example 11 provides trans-N-{4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-phenyl-acetamide hydrochloride melting at 130 - 138°C. Rf(C2) 0.55; FAB-MS: $(M+H)^+$ = 404.

Example 23: trans-N,N-Dimethylamino sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of trans-N-2-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with N,N-dimethylaminosulfonylchloride (0.12 ml) as described in Example 11 provides trans-N,N-Dimethylamino sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 63 - 71 °C. Rf(C1) 0.13; FAB-MS: $(M+H)^+$ = 393.

Example 24: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

A suspention of 2-chloro-quinazolin-4-ylamine (7.02 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (13 g) in 250 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and chromatographed (silica

gel, B2) to give the product as a foam. This material is taken up in dichloromethane (250 ml) and treated at 0 °C with a 4 N HCl solution in dioxane (10 ml). Concentration in vacuo provides a foam which is triturated in boiling cyclohexane to yield after filtration trans-naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 155 - 164°C. Rf(B2) 0.23; FAB-MS: $(M+H)^+$ = 476.

The starting material can be prepared, for example, as follows:

a) trans-{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

A solution of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (17 g) and ethyldiisopropylamine (14.41 ml) in N,N-dimethylformamide (350 ml) is cooled to 0 °C and treated with a solution of naphthalene-1-sulfonylchloride (15.9 g) in N,N-dimethyl formamide (100 ml). The reaction is stirred at ambient temperature for 2 h, concentrated in vacuo. The residue is taken up in dichloromethane, washed with a 0.5 N HCl solution, a saturated aqueous sodium carbonate solution and water, dried and concentrated. Crystallization from hexanes-ethyl acetate gives trans-{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a white powder, melting at 199 - 200 °C. Rf(A1) 0.42.

b) trans-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide

A suspension of trans-{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (25 g) in chloroform (300 ml) is treated with a 4 N HCl solution in dioxane (300 ml) at 0°C. After completion, the reaction mixture is concentrated in vacuo, the residue is taken up in a 1 N aqueous NaOH solution and dichloromethane. After extraction with dichloromethane, the organics are dried over sodium sulfate and concentrated to 18.5 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide as a white powder melting at 157 - 162 °C. Rf(C3) 0.36.

Example 25: trans-{Naphthalene-1-sulfonic acid 4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 24, 0.28 g of 2-chloro-8-methoxy-quinazolin-4-ylamine and 0.444 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl--

cyclohexylmethyl)-amide are reacted together to give trans-naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, melting at 153 - 160 °C. Rf(B2) 0.21; FAB-MS: $(M+H)^+$ = 506.

The starting material can be manufactured, for example, as follows:

2-Chloro-8-methoxy-quinazolin-4-ylamine

A solution of 1 g of 2,4-dichloro-8-methoxy-quinazoline in THF (13 ml) is treated with 0.782 ml of ammonium hydroxide (28 % in water). After completion of the reaction (5 h at ambient temperature), the solution is concentrated in vacuo and the residue is recrystallized twice from dioxane to give 2-chloro-8-methoxy-quinazolin-4-ylamine, melting at 146 - 152 °C. Rf(A1) 0.18.

Example 26: trans-Naphthalene-1-sulfonic acid {4-[(4-amino-6-bromo-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

A suspension of 6-bromo-2-chloro-quinazolin-4-ylamine (1.293 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.662 g) in 50 ml of isopentylalcohol is heated up to 120 °C for 15 h. The resulting solution is concentrated and chromatographed (silica gel, ethyl acetate) to give trans-naphthalene-1-sulfonic acid {4-[(4-amino-6-bromo-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a foam, melting at 233 - 235°C. Rf(A6) 0.36; FAB-MS: $(M+H)^+$ = 554.

Example 27: trans-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 24, 0.28 g of 2-chloro-8-methoxy-quinazolin-4-ylamine and 0.444 g of trans-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide give trans-naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, melting at 130 - 140 °C. Rf(B4) 0.59; FAB-MS: $(M+H)^+$ = 506.

The starting material can be prepared, for example, as follows:

a) trans-{4-[(Naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

According to the procedure described in Example 24a, 5 g of trans-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester and 4.67 g of trans-naphthalene-2-sulfonylchloride give {4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester, melting at 138 - 140 °C. Rf(A4) 0.29.

b) trans-Naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide

According to the procedure described in Example 24b, 5.49 g of trans-{4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester is converted to trans-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide, melting at 123 - 126 °C. Rf(C2) 0.39.

Example 28: trans-Naphthalene-1-sulfonic acid {4-[(4-oxo-3,4-dihydro-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

According to the procedure described in Example 26, 1.36 g of 2-chloro-4 (1H)-quinazolinone and 2.5 g of trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclo-hexylmethyl)-amide give trans-naphthalene-1-sulfonic acid {4-[(4-oxo-3,4-dihydro-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide, melting at 225 - 235 °C. Rf(B2) 0.52; FAB-MS: $(M+H)^+$ = 477.

Example 29: trans-Naphthalene-1-sulfonic acid {4-[(4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

According to the procedure described in Example 24, 0.28 g of 2-chloro-4-phenylamino-quinazoline and 0.26 g of trans-naphthalene-1-sulfonic acid -(4-aminomethyl-cyclohexylmethyl)-amide is converted to yield trans-naphthalene-1-sulfonic acid {4-[(4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide, melting at 145 - 153 °C. Rf(B1) 0.19; FAB-MS: $(M+H)^+$ = 552.

Example 30: trans-Naphthalene-1-sulfonic acid {4-[(4-tert-butylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

A mixture of 2-chloro-4-tert.-butyl-amino-quinazoline (0.118 g) and trans-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.216 g) is heated for 2 min to produce a melt which is dissolved in acetonitrile. 4N HCl in dioxane (0.1 ml) is added and the solvents are removed in vacuo. The residue is dissolved in ethyl acetate and treated with 1N HCl. The aqueous layer is made alkaline with 2 N aqueous NaOH, the product is extracted with ethyl acetate. After concentration in vacuo the residue is redissolved in acetone, 0.1 ml 4N HCl in dioxane is added and crystallization yields trans-naphthalene-1-sulfonic acid {4-[(4-tert.-butylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride, m.p. 238 - 240 °C.

The starting material can be prepared, for example, as follows:

2-Chloro-4-tert.-butylamino-quinazoline

A solution of 2,4-dichloro-quinazoline (2 g) and tert-butylamine (1.46 ml) in isopropanol (5 ml) is heated to 80 °C in a sealed vessel for 30 min. The reaction mixture is concentrated in vacuo and the residue is added to 2 N aqueous NaOH solution and extracted with ethyl acetate. Crystallization from diethylether and hexanes yields 2-chloro-4-tert.-butylamino-quinazoline, m.p. 143 - 145 °C.

Example 31: (R,S)-cis-Naphthalene-1-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Following the procedure described in Example 24, a mixture of 0.259 g of 2-chloro-quinazolin-4-ylamine and 0.48 g of (R,S)-cis-naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl-amide is converted to (R,S)-cis-naphthalene-1-sulfonic acid 3-[(4-amino-quinazolin-2-ylamino)-methyl]-benzylamide hydrochloride melting at 152 - 160 °C. Rf(B2) 0.37; FAB-MS: $(M+H)^+$ = 476.

The starting material can be prepared, for example, as follows:

a) (R,S)-cis-(3-Amino methyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

A solution of 4.0 g of (3-amino methyl-benzyl)-carbamic acid tert-butyl ester in absolute methanol (80 ml) is hydrogenated over Nishimura catalyst (0.8 g) under atmospheric

pressure of hydrogen and at ambient temperature. After completion of the reaction, the catalyst is filtered-off, the filtrate is concentrated and chromatographed on silica gel (C2) to yield (R,S)-cis-(3-amino methyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.33.

b) (R,S)-cis-{3-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

Following the procedure described in Example 24a, a mixture of 1.2 g of (R,S)-cis-(3-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester and 1.12 g of naphthalene-1-sulfonylchloride in acetonitrile are reacted together to yield (R,S)-cis-{3-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester melting at 63 - 68°C. Rf(A4) 0.42.

c) (R,S)-cis-Naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl)-amide

Following the procedure described in Example 24b, (R,S)-cis-{3-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (1.86 g) is converted to (rac.)-cis-naphthalene-1-sulfonic acid (3-aminomethyl-cyclohexylmethyl)-amide as a foam. Rf(C2) 0.50.

Example 32: trans-Naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-ylamino)-cyclohexylethyl]-amide hydrochloride

A solution of 2-chloro-quinazolin-4-ylamine (0.18 g) and trans-naphthalene-1-sulfonic acid (4-aminoethyl-cyclohexylmethyl)-amide (0.345 g) in 6 ml of iso-propanol is stirred at 120 °C for 16h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is purified by flash column chromatography on silica gel (A2 and B2) to yield trans-naphthalene-1-sulfonic acid [4-(4-amino-quinazolin-2-ylamino)-cyclohexylethyl]-amide hydrochloride as colorless amorphous solid; Rf(B2) 0.34, FAB-MS: $(M+H)^+$ = 490.

The starting material can be prepared, for example, as follows:

a) trans-Naphthalene-1-sulfonic acid [(4-hydroxymethyl)-cyclohexylmethyl]-amide

To a suspension of lithium aluminum hydride (4.72 g) in THF (100 ml) is added a solution of trans-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (28.8 g) in THF

(60 ml) in a dropwise manner below 10 °C. The mixture is stirred at room temperature for 1 h and is heated at reflux for 15 h. The resulting mixture is cooled to 0 °C and a mixture of 100 ml of THF and 15 ml of water is carefully added. To the mixture is added 15 ml of 1 N NaOH and the suspension is stirred for 2 h at room temperature. 40 g of magnesium sulfate and 20 g of Celite are added to the mixture and the inorganic solid is removed by filtration. The filtrate is concentrated under reduced pressure and the residual solid is recrystallized from a mixture of THF and isopropanol to give trans-naphthalene-1-sulfonic acid [(4-hydroxymethyl)-cyclohexylmethyl]-amide as a colorless crystals melting at 134 - 135 °C; Rf(A1) 0.25.

b) trans-Naphthalene-1-sulfonic acid {[4-(p-toluenesulfonyl-oxy)-methyl]-cyclohexylmethyl}-amide

To a solution of trans-[(4-hydroxymethyl)-cyclohexylmethyl]-amide (15 g) and triethylamine (12.5 ml) in 200 ml of dichloromethane is added p-toluenesulfonyl chloride (9.86 g) and N,N-dimethylaminopyridine (0.55 g) at room temperature. The mixture is stirred at room temperature for 12 h and is poured into 300 ml of water. The mixture is extracted with dichloromethane. The combined extracts are washed with 0.5 N HCl, aqueous saturated sodium carbonate solution and brine. After drying over sodium sulfate, the solvent is removed under reduced pressure and the residual solid is recrystallized from a mixture of dichloromethane and hexanes to give trans-naphthalene-1-sulfonic acid {[4-(para-toluene sulfonyl)-oxy-methyl]-cyclohexylmethyl}-amide as white crystals melting at 153 - 155 °C; Rf(A1) 0.56.

c) trans-Naphthalene-1-sulfonic acid [(4-cyanomethyl)-cyclohexylmethyl]-amide

To a solution of trans-{[4-(p-toluenesulfonyl)-oxy-methyl]-cyclohexylmethyl}-amide (10.8 g) in N,N-dimethylformamide (100 ml) is added sodium cyanide (4.34 g) at room temperature. The mixture is stirred at 50 °C for 20 h. After cooling to room temperature, N,N-dimethylformamide is removed under reduced pressure. The residue is suspended in water and is extracted with ethyl acetate. The combined extracts are washed with water and brine and are dried over sodium sulfate. The solvent is removed under reduced pressure and the residual solid is recrystallized from a mixture of dichloromethane and hexanes to give trans-naphthalene-1-sulfonic acid [(4-cyanomethyl)-cyclohexylmethyl]-amide as colorless crystals melting at 136 - 138 °C; Rf(A1) 0.50, FAB-MS: $(M+H)^+ = 343$.

d) trans-Naphthalene-1-sulfonic acid [(4-aminoethyl)-cyclohexylmethyl]-amide

A suspension of naphthalene-1-sulfonic acid trans-[(4-cyanomethyl)-cyclohexylmethyl]-amide (2.0 g) and Raney nickel (0.5 g) in methanol (50 ml) containing 5% ammonia is stirred under hydrogen at room temperature for 16 h. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. To the residue is added 4 N HCl in dioxane (10 ml) at 0 °C and the resulting solution is stirred for 30 min. The mixture is concentrated under reduced pressure and the residual solid is washed with diethylether. To the solid is added 1 N NaOH (25 ml) solution and the mixture is extracted with dichloromethane. The combined extracts are dried over sodium sulfate and are concentrated under reduced pressure to give naphthalene-1-sulfonic acid trans-[(4-aminoethyl)-cyclohexylmethyl]-amide as white amorphous solid; Rf(B3) 0.46, FAB-MS: $(M+H)^+ = 347$.

Example 33: In a manner analogous to that described herein before it is also possible to manufacture the following compounds:

Naphthalene-1-sulfonic acid {4-{[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{{4-[2-(2-hydroxyethyl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{{4-[2-(morpholin-1-yl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{{4-[1,1 -di(hydroxymethyl)-methylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-methylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-(N,N-dimethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-yl)-methyl-amino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methyl-amide.

cis-Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-(acetylamino)-benzenesulfonamide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-trifluoromethyl-benzenesulfonamide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide.

Quinoline-8-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide.

Cyclohexane-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

2-Methoxyethane sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Morpholine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

4-Methyl-piperazine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N,N-Dimethylaminosulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-Methylaminosulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxyethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-amino-8-(N,N-dimethylaminoethoxy)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-{[4-amino-8-(morpholin-4-ylethoxy)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-8-ethyl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxyethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-1-sulfonic acid {4-[(4-amino-5,8-dimethoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Piperidine-1-sulfonic acid {3-[(4-amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

Naphthalene-2-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide.

N-{3-[(4-Amino-8-methoxy-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide.

Naphthalene-2-sulfonic acid {3-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclopentylmethyl}-amide.

8-Methoxy-2-[4-(naphthalen-ylmethanesulfonylmethyl)-cyclohexylmethyl]-quinazoline-2,4-diamine.

4-(Chloro-phenylamino)-8-methoxy-2-(4-pyrrolidin-1-ylmethyl-cyclohexylamino)-quinazoline

4-(Chloro-phenyl)-8-methoxy-2-methyl-2-(4-pyrrolidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine

1-{4-[4-(4-Chloro-phenyl)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-pyrrolidin-2-one

{4-[4-(4-Chloro-phenyl)-6-dimethylamino-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide

2-{4-(4-Chloro-phenylamino)-2-[4-(propane-2-sulfonylmethyl)-cyclohexylamino]-quinazolin-8-yloxy]-ethanol

2-{6-Chloro-4-(4-chloro-phenylamino)-2-[4-(propane-2-sulfonylmethyl)-cyclohexylamino]-quinazolin-8-yloxy]-ethanol

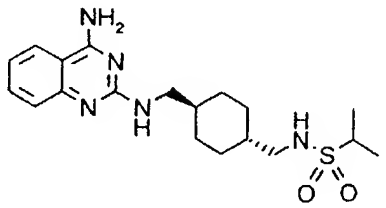
6-Chloro-4-(4-Chloro-phenyl)-8-(2-methoxy-ethoxy)-2-{4-[2-(propane-2-sulfonyl)-ethyl]-cyclohexyl}-quinazoline-2,4-diamine

2-{4-[8-(2-Dimethylamino-ethoxy)-4-(4-fluoro-phenylamino)-quinazolin-2-ylamino]-cyclohexyl}-ethanesulfonic acid dimethylamide

N,N-Dimethylsulfonic acid 4-[4-(4-chloro-phenylamino)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-amide

3-{4-[4-(4-Chloro-phenylamino)-8-(2-hydroxy-ethoxy)-quinazolin-2-ylamino]-cyclohexyl}-1-(4-methyl-piperazin-1-yl)-propan-1-one

Example 34: *trans*-Propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride



A solution of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.5 g) and diisopropylethylamine (1.19 ml) in 6 ml of N,N-dimethylformamide is cooled to 0 °C and treated with isopropyl-sulfonylchloride (1.09 ml) in N,N-dimethylformamide (1 ml). After completion, the reaction mixture is concentrated and the residue is chromatographed (silica gel, C1) to give the product as a foam. It is taken up in dichloromethane (2 ml) and treated at 0 °C with a 4 N HCl in dioxane (2 ml). Concentration in vacuo followed by crystallization from acetonitrile yields *trans*-propane-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 120-130 °C. Rf(C1) 0.21; FAB-MS: $(M+H)^+$= 392.

The starting material can be prepared, for example, as follows:

a) *trans*-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

A solution of *trans*-4-(tert-butoxycarbonylamino-methyl)-cyclohexanecarboxylic acid (EP 0614 911 A1) (34.5 g) and triethylamine (28 ml) in dichloromethane (700 ml) is cooled to -70 °C and treated with methylchloroformate (12.9 ml). The reaction mixture is stirred 0.5 h at -70 °C. The temperature is allowed to increase to 0 °C and the solution is stirred another 0.5 h until completion of the reaction. The reaction mixture is taken up in ice-cold dichloromethane, washed with an ice-cold 0.5 N HCl solution, a saturated aqueous sodium

carbonate solution and water. The organics are dried over sodium sulfate and concentrated to 41.3 g of mixt-anhydride as an oil. This material is taken up in THF and treated at - 70 °C with sodium borohydride (5.90 g), followed by absolute methanol (10 ml). The reaction mixture is stirred 15 h at 0 °C and 1 h at ambient temperature to drive the reaction to completion. A 0.5 N HCl solution is then carefuly added at 0 °C, followed by ethyl acetate. The organics are washed with a saturated aqueous sodium carbonate solution, water, dried over sodium sulfate and concentrated. Chromatography on silica gel (A1) yields *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as a white powder, melting at 88 - 89 °C. Rf(A1) 0.24.

b) *trans*-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

trans-(4-Hydroxymethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in pyridine (200 ml) at 0 °C is treated with a solution of para-toluenesulfonylchloride (24.44 g) in pyridine (50 ml). The mixture is stirred at 0 °C until completion of the reaction and concentrated in vacuo. The residue is taken up in ethyl acetate, washed with water and dried over sodium sulfate. Concentration of the solution yields the tosylate, used without further purification. This material is treated with sodium azide (19.23 g) in N,N-dimethylformamide (800 ml) at 50 °C. After completion of the reaction, the solution is concentrated and the resulting paste is taken up in dichloromethane, washed with water and concentrated. Chromatography of the crude material on silica gel (A2 then A3) gives *trans*-(4-azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(A3) 0.33; IR (dichloromethane) ν max 2099 cm^{-1}.

c) *trans*-(4-Aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester

trans-(4-Azidomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester (24 g) in ethyl acetate (1 liter) is hydrogenated over platinumoxide (2.4 g) at ambient temperature under atmospheric pressure of hydrogen. The catalyst is filtered off and the filtrate concentrated to yield *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester as an oil. Rf(C2) 0.41.

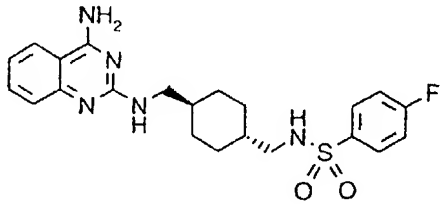
d) *trans*-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester

A suspention of 5.0 g of 2-chloro-quinazolin-4-ylamine and 6.75 g of *trans*-(4-aminomethyl-cyclohexylmethyl)-carbamic acid tert-butyl ester in isopentylalcohol (120 ml) is heated up to 120 °C for 15 h. The reaction mixture is concentrated and chromatographed on silica gel (B1 then B2) to give *trans*-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester as a foam. Rf(B2) 0.33.

e) *trans*-N(2)-(4-Aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride

A solution of *trans*-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-carbamic acid tert-butyl ester (9.58 g) in dichloromethane (130 ml) is cooled to 0 °C and treated with a 4N HCl solution in dioxane (130 ml). After completion, the reaction mixture is concentrated in vacuo to yield *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride melting at 189 - 192 °C. Rf(C3) 0.54.

Example 35: *trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide hydrochloride

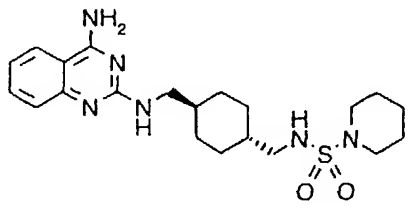


Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 4-fluorobenzenesulfonylchloride (0.326 g) as described in Example 34 gives *trans*-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-4-fluoro-benzenesulfonamide hydrochloride as a powder melting at 95-102 °C. Rf(B2) 0.30; FAB-MS: $(M+H)^+$= 444.

Example 36: *trans*-N-{4-[(4-Amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide hydrochloride

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.5 g) with 2-nitrobenzenesulfonylchloride (0.433 g) as described in 34 gives *trans*-N-{4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-2-nitro-benzenesulfonamide hydrochloride as a powder melting at 129-138 °C. Rf(C1) 0.15; FAB-MS: $(M+H)^+$= 471.

Example 37: *trans*-Piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride



Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 0.246 g of piperidinesulfonylchloride (WO 94/05639) as described in Example 34 gives *trans*-piperidine-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a powder melting at 92-95 °C. Rf(C3) 0.70; FAB-MS: $(M+H)^+$= 433.

Example 38: *trans*-Morpholine-4-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-quinazoline-2,4-diamine hydrochloride (0.4 g) with 0.311 g of 4-morpholinesulfonylchloride (WO 94/05639) as described in Example 34 gives *trans*-morpholine-4-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride hydrochloride as a powder melting at 125 °C. Rf(C2) 0.41; FAB-MS: $(M+H)^+$= 435.

Example 39: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

A suspention of (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine ((0.37 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.518 g) in isopentylalcohol (10 ml) is heated to 120 °C for 18 h. The reaction mixture is concentrated and the residue is chromatographed (silica gel, B1) to give *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 105-110 °C. Rf(B2) 0.33; FAB-MS: $(M+H)^+$= 534.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine

A solution of 2,4-dichloro-quinazoline (5 g) and diisopropylethylamine (8.6 ml) in isopropanol (30 ml) is treated with 2-methoxyethylamine (2.07 g) in isopropanol (10 ml). Under completion of the reaction (exothermic), the crude mixture is concentrated and the residue partitioned between water and dichloromethane. The aqueous phase is extracted with dichloromethane, the organics are combined and dried over magnesium sulfate. Chromatography (silica gel, A4 followed by A1) gives (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine as a powder melting at 122-125 °C. Rf(A1) 0.52.

Example 40: *trans*-Naphthalene-2-sulfonic acid {4-{[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-methoxy-ethyl)-amine (0.37 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.518 g) (see Example 27b for preparation) according to Example 40, followed by chromatography (silica gel, B1) gives *trans*-naphthalene-2-sulfonic acid {4-{[4-(2-methoxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a foam melting at 101-106 °C. Rf(B2) 0.36; FAB-MS: $(M+H)^+$= 534.

Example 41: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-ethanol (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.446 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-hydroxy-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a foam melting at 107-110 °C. Rf(C1) 0.05; FAB-MS: $(M+H)^+$= 520.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-ethanol

The reaction of 2,4-dichloro-quinazoline (5 g) and ethanolamine (1.68 g) according to Example 40a, followed by crystallization from dichloromethane gives 2-(2-chloro-quinazolin-4-ylamino)-ethanol as a white powder melting at 173-177 °C. Rf(A8) 0.26.

Example 42: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-propane-1,3-diol (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.524 g) according to Example 40, followed by chromatography (silica gel, C2) and crystallization from acetonitrile gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-hydroxy-1-hydroxymethyl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a white powder melting at 186-188 °C. Rf(C2) 0.24; FAB-MS: $(M+H)^+$= 550.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-propane-1,3-diol

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-amino-1,3-propane-diol (4.12 g) in methanol according to the procedure described in Example 40a, followed by crystallization from methanol gives 2-(2-chloro-quinazolin-4-ylamino)-propane-1,3-diol as a white powder melting at 185-186 °C. Rf(A6) 0.17.

Example 43: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of 2-(2-chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine (0.35 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.462 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(3-methoxy-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 82-85 °C. Rf(C1) 0.20; FAB-MS: $(M+H)^+$= 548.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine

The reaction of 2,4-dichloro-quinazoline (9 g) and 3-methoxy-propylamine (4.03 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, A4) gives 2-(2-chloro-quinazolin-4-yl)-(3-methoxy-propyl)-amine as a white powder melting at 89-90 °C. Rf(A4) 0.20.

Example 44: *trans*-Naphthalene-1-sulfonic acid {4-{[4-[2-(2-hydroxy-ethoxy)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide

The reaction of 2-[2-(2-chloro-quinazolin-4-ylamino)-ethoxy]-ethanol (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.497 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-[2-(2-hydroxy-ethoxy)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide as a powder melting at 90-92 °C. Rf(C1) 0.09; FAB-MS: $(M+H)^+$= 564.

The starting material can be prepared, for example, as follows:

2-[2-(2-Chloro-quinazolin-4-ylamino)-ethoxy]-ethanol

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-(2-aminoethoxy)-ethanol (4.75 g) according to the procedure described in Example 40a, followed by crystallization from diethylether gives 2-[2-(2-chloro-quinazolin-4-ylamino)-ethoxy]-ethanol as a white powder melting at 108-109 °C. Rf(A8) 0.12.

Example 45: *trans*-Naphthalene-1-sulfonic acid {4-[(4-methylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-methyl-amine (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.515 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[(4-methylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a tan foam melting at 100-110 °C. Rf(C1) 0.16; FAB-MS: $(M+H)^+$= 490.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-methyl-amine

2,4-Dichloro-quinazoline (22 g) in THF (330 ml) is treated with a 40% aqueous solution of methylamine (24.85 ml). Upon completion of the reaction (exothermic) the crude mixture is concentrated *in vacuo* and the residue triturated in dioxane. Crystallization from water gives (2-chloro-quinazolin-4-yl)-methyl-amine as a white powder melting at 212-214 °C. Rf(A1) 0.41.

Example 46: *trans*-Naphthalene-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-dimethyl-amine (0.3 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.48 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-[(4-dimethylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a powder melting at 87-94 °C. Rf(C1) 0.32; FAB-MS: $(M+H)^+$= 504.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-dimethyl-amine

2,4-Dichloro-quinazoline (7 g) in THF (100 ml) is treated with a 40% aqueous solution of dimethylamine (11.57 ml). Upon completion of the reaction (exothermic), concentration *in vacuo*, followed by aqueous work-up and chromatography (silica gel, dichloromethane) (2-chloro-quinazolin-4-yl)-dimethyl-amine is obtained as a powder melting at 112-114 °C. Rf(dichloromethane) 0.12.

Example 47: *trans*-Naphthalene-1-sulfonic acid {4-[(4-morpholin-4-yl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide

The reaction of 2-chloro-4-morpholin-4-yl-quinazoline (0.4 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.533 g) according to Example 40, followed by chromatography (silica gel, C4) gives *trans*-naphthalene-1-sulfonic acid {4-[(4-morpholin-4-yl-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide as a powder melting at 95-100 °C. Rf(C6) 0.24; FAB-MS: $(M+H)^+$= 546.

The starting material can be prepared, for example, as follows:

2-Chloro-4-morpholin-4-yl-quinazoline

The reaction of 2,4-dichloro-quinazoline (9 g) and morpholine (3.93 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, A4) gives 2-chloro-4-morpholin-4-yl-quinazoline as a white powder melting at 112-113 °C. Rf(A4) 0.30.

Example 48: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(4-methyl-piperazin-1-yl)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

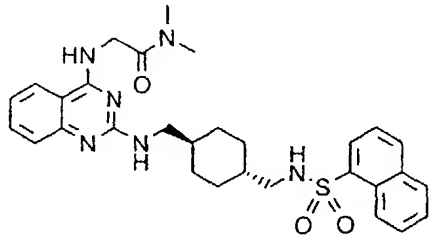
The reaction of 2-chloro-4-(4-methyl-piperazin-1-yl)-quinazoline (1 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.39 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(4-methyl-piperazin-1-yl)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 103-107 °C. Rf(B4) 0.46; ESI-MS: $(M+H)^+$= 559.

The starting material can be prepared, for example, as follows:

2-Chloro-(4-methoxy-piperidin-1-yl)-quinazoline

The reaction of 2,4-dichloro-quinazoline (10 g) and 1-methylpiperazine (6.14 ml) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives 2-chloro-4-(4-methyl-piperazin-1-yl)-quinazoline as a powder melting at 83-84 °C. Rf(B2) 0.54.

Example 49: *trans*-N,N-Dimethyl-2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-acetamide



The reaction of 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide (1.5 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.07 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-N,N-dimethyl-2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-acetamide as a powder melting at 132-143 °C. Rf(C1) 0.35; ESI-MS: $(M+H)^+$= 561.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide

The reaction of 2,4-dichloro-quinazoline (10 g) and 2-amino-N,N-dimethyl-acetamide (5.64 g) according to the procedure described in Example 40a, followed by trituration in boiling hexanes gives 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide as a powder melting at 190-192 °C. Rf(A1) 0.10.

Example 50: *trans*-N,N-Dimethyl-2-{2-{{4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-acetamide

The reaction of 2-(2-chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide (1 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.38 g) according to Example 40, followed by chromatography (silica gel, B4) gives *trans*-N,N-dimethyl-2-{2-{{4-[(naphthalene-2-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-acetamide as a powder melting at 124-131 °C. Rf(B4) 0.56; ESI-MS: $(M+H)^+$= 561.

Example 51: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-piperidin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine (0.6 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.857 g) according to Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-piperidin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 116-120 °C. Rf(C1) 0.20; ESI-MS: $(M+H)^+$= 587.

The starting material can be prepared, for example, as follows:

2-(2-Chloro-quinazolin-4-ylamino)-N,N-dimethyl-acetamide

The reaction of 2,4-dichloro-quinazoline (9 g) and 2-piperidino-ethylamine (5.79 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives (2-chloro-quinazolin-4-yl)-(2-piperidin-1-yl-ethyl)-amine as a powder melting at 117-120 °C. Rf(B2) 0.26.

Example 52: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine (0.7 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.994 g) according to

Example 40, followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-morpholin-4-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 114-119 °C. Rf(C1) 0.18; ESI-MS: $(M+H)^+$= 589.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine

The reaction of 2,4-dichloro-quinazoline (9 g) and 4-(2-aminoethyl)-morpholine (5.88 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, C1) gives (2-chloro-quinazolin-4-yl)-(2-morpholin-4-yl-ethyl)-amine as a powder melting at 106-108 °C. Rf(C1) 0.31.

Example 53: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide hydrochloride

The reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine (1.5 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.35 g) according to Example 40, followed by chromatography (silica gel, C2) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide hydrochloride as a powder melting at 130-140 °C. Rf(C2) 0.22; ESI-MS: $(M+H)^+$= 561.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine

The reaction of 2,4-dichloro-quinazoline (10 g) and 3-dimethylamino-1-propylamine (5.13 g) according to the procedure described in Example 40a, followed by chromatography (silica gel, B4 then B5) gives N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine as a powder melting at 64-72 °C. Rf(B2) 0.10.

Example 54: *trans*-Naphthalene-2-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

A solution of N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (0.4 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.682 g) in isopentylalcohol (50 ml) was heated to 80 °C for 4 h, then concentrated *in vacuo*. Aqueous

work-up followed by chromatography (silica gel, C1) gives *trans*-naphthalene-2-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 96 °C. Rf(C2) 0.32; ESI-MS: $(M+H)^+$= 547. Analysis for $C_{30}H_{38}N_6O_2S+0.5H_2O$: C 64.8%; H 7.1%; N 15.1%; S 5.8%; O 7.2%, found: C 64.2%; H 6.9%; N 14.9%; S 5.6%; O 6.8%.

The starting material can be prepared, for example, as follows:

N-(2-Fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

A solution of 2,4-difluoro-quinazoline (0.85 g) (prepared from 2,4-dichloro-quinazoline according to: Schroeder, H. *et al. J. Org. Chem.* **1962**, *27*, 2580) in N,N-dimethylformamide (25 ml) is treated with a solution of 2-dimethylaminoethylamine (0.84 ml) of in N,N-dimethylformamide (5 ml) at 0 °C. After completion of the reaction (0.25 h at 0 °C), the reaction mixture is concentrated *in vacuo* and the residue is chromatographed (silica gel, B2) to give N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine as a powder melting at 103-106 °C. Rf(B2) 0.22.

Example 55: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Reaction of N-(2-fluoro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (1.26 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.14 g) according to Example 54 followed by chromatography (silica gel, C1) and crystallization from isopropylether gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 112-115 °C. Rf(C2) 0.40; ESI-MS: $(M+H)^+$= 547. Analysis for $C_{30}H_{38}N_6O_2S+0.5H_2O$: C 64.8%; H 7.1%; N 15.1%; S 5.8%; O 7.2%, found: C 63.3%; H 7.0%; N 15.2%; S 5.5%; O 8.6%.

Example 56: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-diethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

A mixture of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride (3 g), *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (3.48 g), diisopropylethylamine (4.9 ml) and phenol (13.4 g) is heated to 150 °C for 3 h to produce a

melt. The reaction mixture is taken up in dichloromethane, washed with a 1N aqueous sodium hydroxide solution, brine and dried over sodium sulfate. Concentration *in vacuo* followed by crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-diethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 160-162 °C. Rf(C2) 0.38; ESI-MS: $(M+H)^+$= 575.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride

A suspension of 2,4-dichloro-quinazoline (30 g) in isopropanol (200 ml) is treated by dropwise addition of a solution of N,N-diethylethylenediamine (23.3 ml) in isopropanol (50 ml) in an exothermic reaction. The reaction mixture is cooled to 0 °C, the voluminous precipitate is collected by suction filtration and dried *in vacuo* to give N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride as a powder melting at 205-206 °C. Rf(B2) 0.20.

Example 57: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-1,1-dimethyl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Reaction of N(2)-(2-chloro-quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine (0.6 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.716 g) according to Example 56 followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-1,1-dimethyl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 89-93 °C. Rf(C1) 0.28; ESI-MS: $(M+H)^+$= 575.

The starting material can be prepared, for example, as follows:

N(2)-(2-Chloro-quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine

The reaction of 2,4-dichloro-quinazoline (9.07 g) and 2-dimethylamino-1,1-dimethyl-ethylamine (5.3 g) (prepared from 1-dimethylamino-2-methyl-2-nitropropane, see: Johnson, H. G. *J. Am. Chem. Soc.* **1946**, *68*, 12 and Freifelder, M. *et al. J. Org. Chem.* **1965**, *30*, 4370) according to the procedure described in Example 56a, followed by an aqueous sodium bicarbonate wash and chromatography (silica gel, B1) gives N(2)-(2-chloro-

quinazolin-4-yl)-2,N(1),N(1)-trimethyl-propane-1,2-diamine as a powder melting at 92-95 °C. Rf(B1) 0.36.

Example 58: *trans*-Naphthalene-1-sulfonic acid {4-{[4-[2-(4-methyl-piperazin-1-yl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide

The reaction of (2-chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine (0.8 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (1.08 g) according to Example 40, followed by chromatography (silica gel, E2) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-[2-(4-methyl-piperazin-1-yl)-ethylamino]-quinazolin-2-ylamino}-methyl}-cyclohexylmethyl}-amide as a powder melting at 107-110 °C. Rf(E2) 0.64; ESI-MS: $(M+H)^+$= 602.

The starting material can be prepared, for example, as follows:

(2-Chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine

The reaction of 2,4-dichloro-quinazoline (7 g) and 2-(4-methyl-piperazin-1-yl)-ethylamine (5.03 g)(*Bull. Soc. Chim. France* **1962**, 556) according to the procedure described in Example 40a, followed by chromatography (silica gel, B2) gives (2-chloro-quinazolin-4-yl)-[2-(4-methyl-piperazin-1-yl)-ethyl]-amine as a powder melting at 58-60 °C. Rf(B2) 0.15.

Example 59: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride (2 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (2.22 g) according to Example 56 followed by crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 135-136 °C. Rf(C2) 0.19; ESI-MS: $(M+H)^+$= 589.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-quinazoline (30 g) and N,N-diethyl-1,3-diamino-propane (26.1 ml) according to the procedure described in Example 56a, followed by crystallization from

isopropylether/isopropanol gives N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine as a powder melting at 163-164 °C. Rf(C2) 0.32.

Example 60: *trans*-Propane-2-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

A solution of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and diisopropylethylamine (0.39 ml) in N,N-dimethylformamide is treated with a solution of isopropylsulfonylchloride (0.125 ml) in acetonitrile. Upon completion of the reaction, the solution is concentrated *in vacuo* and the residue is chromatographed (silica gel, C2) to give *trans*-propane-2-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a yellow powder melting at 50-53 °C. Rf(C2) 0.27; ESI-MS: $(M+H)^+$= 505.

The starting material can be prepared, for example, as follows:

trans-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine

A mixture of N-(2-chloro-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine (3 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (6.48 g) (Lancaster, >98% *trans*) as a paste is heated up for 3 minutes to produce a melt. Chromatography (silica gel, C3) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine as a glass. Rf(C3) 0.15; ESI-MS: $(M+H)^+$= 399.

Example 61: *trans*-4-Methyl-piperazine-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and 4-methyl-piperazin-1-ylsulfonylchloride hydrochloride (0.212 g) (WO92/13545) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-4-methyl-piperazine-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a yellow powder melting at 75-77 °C. Rf(C2) 0.29; ESI-MS: $(M+H)^+$= 561.

Example 62: *trans*-N-{4-{[4-(3-Diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-C-phenylmethanesulfonamide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-diethylamino-propyl)-quinazoline-2,4-diamine (0.3 g) and phenylmethanesulfonylchloride (0.172 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-N-{4-{[4-(3-diethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-C-phenylmethanesulfonamide as a white powder melting at 62-63 °C. Rf(C2) 0.23; ESI-MS: $(M+H)^+$= 553.

Example 63: *trans*-Naphthalene-2-sulfonic acid {4-{[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.4 g) and naphthalene-2-sulfonylchloride (0.367 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-naphthalene-2-sulfonic acid {4-{[4-(3-dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 83-86 °C. Rf(C2) 0.34; ESI-MS: $(M+H)^+$= 561.

The starting material can be prepared, for example, as follows:

trans-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine

Reaction of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-propane-1,3-diamine (2.5 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (5.9 g) according to Example 60a followed by chromatography (silica gel, C3) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine as a foam. Rf(C3) 0.24.

Example 64: *trans*-N-{4-{[4-(3-Dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-4-fluoro-benzenesulfonamide

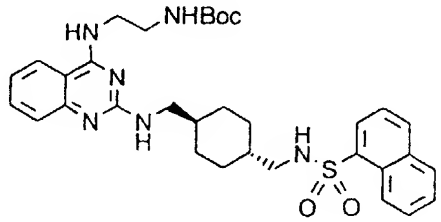
The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.4 g) and 4-fluoro-benzenesulfonylchloride (0.315 g) as described in Example 60 followed by chromatography (silica gel, C2) gives *trans*-N-{4-{[4-(3-

dimethylamino-propylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-4-fluoro-benzenesulfonamide as a powder melting at 74-79 °C. Rf(C2) 0.30; ESI-MS: $(M+H)^+$= 529.

Example 65: *trans*-N(4)-(3-Dimethylamino-propyl)-N(2)-{4-[(2-methoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine

Reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(3-dimethylamino-propyl)-quinazoline-2,4-diamine (0.5 g) and 2-methoxy-benzylbromide (0.462 g) (Kelly, J. L. *et al J. Med. Chem.* **1989**, *32*, 1757) in N,N-dimethylformamide (11 ml) in the presence of diisopropylethylamine (0.693 ml) at ambient temperature followed by chromatography (silica gel, C3) gives *trans*-N(4)-(3-dimethylamino-propyl)-N(2)-{4-[(2-methoxy-benzylamino)-methyl]-cyclohexylmethyl}-quinazoline-2,4-diamine as a foam melting at 134-140 °C. Rf(C3) 0.28; ESI-MS: $(M+H)^+$= 491.

Example 66: *trans*-{2-{2-{{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino}-ethyl}-carbamic acid tert-butyl ester



An homogeneous mixture of [2-(2-chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester (0.5 g) and of *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl-methyl)-amide (0.463 g) is stirred at 200 °C. Upon completion of the reaction the product is chromatographed (silica gel, B2) to give *trans*-{2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino}-ethyl}-carbamic acid *tert*-butyl ester as a powder melting at 123-127 °C. Rf(B2) 0.32; ESI-MS: $(M+H)^+$= 619.

The starting material can be prepared, for example, as follows:

[2-(2-Chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester

The reaction of 2,4-dichloro-quinazoline (3.72 g) and N-BOC-ethylenediamine (3 g) according to the procedure described in Example 56a, followed by chromatography (silica

gel, A1) gives [2-(2-chloro-quinazolin-4-ylamino)-ethyl]-carbamic acid *tert*-butyl ester as a white foam. Rf(A1) 0.36.

Example 67: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-amino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

A solution of *trans*-{2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}quinazolin-4-ylamino}-ethyl}-carbamic acid *tert*-butyl ester (0.52 g) in dichloromethane (20 ml) is cooled to 0 °C and treated by slow addition of trifluoroacetic acid (20 ml). Upon completion of the reaction, the solution is concentrated *in vacuo* and the residue is chromatographed (silica gel, C3) to give *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-amino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a foam melting at 125-130 °C. Rf(C3) 0.54; ESI-MS: $(M+H)^+$= 519.

Example 68: *trans*-4-{2-{2-{{4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester

The reaction of 4-[2-(2-chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester (0.45 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-amide (0.349 g) according to the procedure described in Example 66, followed by chromatography (silica gel, B2) gives *trans*-4-{2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester as a foam melting at 115-120 °C. Rf(B2) 0.29; ESI-MS: $(M+H)^+$= 689.

The starting material can be prepared, for example, as follows:

4-[2-(2-Chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester

The reaction of 2,4-dichloro-quinazoline (1.73 g) and 4-(2-amino-ethyl)-piperazine-1-carboxylic acid *tert*-butyl ester (2 g) (prepared from 1-(2-aminoethyl)-piperazine according to: Prugh, J. D. *et al Synth. Comm.* **1992**, *22*, 2357) according to the procedure described in Example 56a, followed by chromatography (silica gel, B1) gives 4-[2-(2-chloro-quinazolin-4-ylamino)-ethyl]-piperazine-1-carboxylic acid *tert*-butyl ester as a foam. Rf(B1) 0.19.

Example 69: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-piperazin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Treatment of *trans*-4-{2-{2-{{4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexylmethyl}-amino}-quinazolin-4-ylamino}-ethyl}-piperazine-1-carboxylic acid *tert*-butyl ester (0.396 g) with trifluoroacetic acid according to Example 67 followed by chromatography (silica gel, C3) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-piperazin-1-yl-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide melting at 135-139 °C. Rf(C3) 0.50; ESI-MS: $(M+H)^+$= 588.

Example 70: *trans*-Naphthalene-1-sulfonic acid {4-{[4-[(2-dimethylamino-ethyl)-methyl-amino]-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

The reaction of *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine (0.3 g) and naphthalene-1-sulfonylchloride (0.275 g) as described in Example 60 followed by chromatography (silica gel, C1) gives *trans*-naphthalene-1-sulfonic acid {4-{[4-[(2-dimethylamino-ethyl)-methyl-amino]-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide as a powder melting at 70-72 °C. Rf(C1) 0.15; ESI-MS: $(M+H)^+$= 561.

The starting material can be prepared, for example, as follows:

a) N-(2-Chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-quinazoline (15 g) and N,N,N'-trimethylethyenediamine (7.7 g) according to the procedure described in Example 56a, followed by crystallization from isopropanol gives N-(2-chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride as a white powder melting at 163-165 °C. Rf(B2) 0.60.

b) *trans*-N(2)-(4-Aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine

Reaction of N-(2-chloro-quinazolin-4-yl)-N,N',N'-trimethyl-ethane-1,3-diamine hydrochloride (1.4 g) and *trans*-1,4-cyclohexane-bis-(methylamine) (3.3 g) according to Example 60a followed by chromatography (silica gel, C2) gives *trans*-N(2)-(4-aminomethyl-cyclohexylmethyl)-N(4)-(2-dimethylamino-ethyl)-N(4)-methyl-quinazoline-2,4-diamine as an oil. Rf(C2) 0.06.

Example 71: *trans*-Naphthalene-1-sulfonic acid {4-{[4-amino-quinazolin-2-yl]-methyl-amino]-methyl}-cyclohexylmethyl}-amide hydrochloride

Reaction of 2-chloro-quinazolin-4-yl-amine (0.267 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.515 g) according to Example 56 gives *trans*-naphthalene-1-sulfonic acid {4-{[4-amino-quinazolin-2-yl]-methyl-amino]-methyl}-cyclohexylmethyl}-amide hydrochloride melting at 175-180 °C. Rf(C1) 0.62; ESI-MS: $(M+H)^+ = 490$.

The starting material can be prepared, for example, as follows:

a) *trans*-4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride

A suspension of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid (45 g) (prepared as described in Example 38a) in toluene (550 ml) is treated with oxalylchloride (33.4 ml) and 2 drops of N,N-dimethylformamide. The mixture is stirred at 70 °C for 2 h and the resulting solution is concentrated *in vacuo*. The residue is stirred in toluene (200 ml) and cooled to 0 °C. The solids are collected by suction filtration and dried *in vacuo* at 50 °C to give *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride as a white powder melting at 140-142 °C.

b) *trans*-4-[(Naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide

A mixture of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarbonyl chloride (42.5 g) and potassiumcarbonate (17.66 g) in dichloromethane (1.2 l) and water (120 ml) is cooled to 5 °C and treated with 11 ml of a methylamine solution (40% in water). Upon completion (30 min at 5 °C) the reaction mixture is partitioned between water and dichloromethane. The organics are concentrated *in vacuo* to give *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide as a white powder melting at 176-177 °C.

c) *trans*-Naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide

Reaction of *trans*-4-[(naphthalene-1-sulfonylamino)-methyl]-cyclohexanecarboxylic acid methylamide (0.83 g) with borane-THF complex according to Example 5c gives *trans*-

naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide as a white powder melting at 141-142 °C. Rf(C2) 0.14.

Example 72: *trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-6-fluoro-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide

Reaction of 2-chloro-6-fluoro-quinazolin-4-yl-amine (0.26 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.437 g) according to Example 26 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-6-fluoro-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide melting at 118-122 °C. Rf(C1) 0.22; ESI-MS: $(M+H)^+$= 494.

The starting material can be prepared, for example, as follows:

2-Chloro-6-fluoro-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-6-fluoro-quinazoline (3 g) (WO 95/32205) and ammonium hydroxide according to Example 25a gives 2-chloro-6-fluoro-quinazolin-4-yl-amine melting at 165-167 °C. Rf(A5) 0.13.

Example 73: *trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of 2-chloro-6-methoxy-quinazolin-4-yl-amine (0.5 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.793 g) according to Example 24 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-6-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 210-212 °C. Rf(C1) 0.11; ESI-MS: $(M+H)^+$= 506.

The starting material can be prepared, for example, as follows:

2-Chloro-6-methoxy-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-6-methoxy-quinazoline (1.3 g) and ammonium hydroxide according to Example 25a gives 2-chloro-6-methoxy-quinazolin-4-yl-amine melting at 167-171 °C. Rf(A1) 0.24.

Example 74: *trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-5-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride

Reaction of 2-chloro-5-methoxy-quinazolin-4-yl-amine (0.25 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (0.397 g) according to Example 24 gives *trans*-naphthalene-1-sulfonic acid {4-[(4-amino-5-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexylmethyl}-amide hydrochloride melting at 238-241 °C. Rf(C1) 0.11; ESI-MS: $(M+H)^+$= 506.

The starting material can be prepared, for example, as follows:

2-Chloro-5-methoxy-quinazolin-4-yl-amine

Reaction of 2,4-dichloro-5-methoxy-quinazoline (0.8 g) and ammonium hydroxide according to Example 25a gives 2-chloro-5-methoxy-quinazolin-4-yl-amine melting at 220-230 °C. Rf(A1) 0.24.

Example 75: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (1 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (1.42 g) according to Example 56 followed by chromatography (silica gel, C2) and crystallization from isopropylether/isopropanol gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-dimethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide melting at 112-115 °C. Rf(C2) 0.36; ESI-MS: $(M+H)^+$= 578.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine

Reaction of 2,4-dichloro-8-methoxy-quinazoline (10 g) and 2-dimethylaminoethylamine (4.76 ml) according to Example 40a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine melting at 176-178 °C. Rf(B2) 0.24.

Example 76: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(2-diethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide

Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride (2g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (2.12 g) according to Example 56 gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(2-diethylamino-ethylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide melting at 109-114 °C. Rf(C2) 0.44; ESI-MS: $(M+H)^+$= 605.

The starting material can be prepared, for example, as follows:

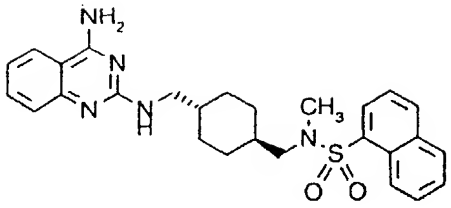
N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride
Reaction of 2,4-dichloro-8-methoxy-quinazoline (25 g) and 2-diethylaminoethylamine(18.9 ml) according to Example 56a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-ethane-1,2-diamine hydrochloride melting at 189-190 °C. Rf(C2) 0.53.

Example 77: *trans*-Naphthalene-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide hydrochloride
Reaction of N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride (2 g) and *trans*-naphthalene-1-sulfonic acid (4-methylaminomethyl-cyclohexylmethyl)-amide (2.03 g) according to Example 56 followed by chromatography (silica gel, C2), treatment with a 4N HCl solution in dioxane and trituration of the crude material in isopropylether gives *trans*-naphthalene-1-sulfonic acid {4-{[4-(3-diethylamino-propylamino)-8-methoxy-quinazolin-2-ylamino]-methyl}-cyclohexylmethyl}-amide hydrochloride melting at 155 °C. Rf(C2) 0.30; ESI-MS: $(M+H)^+$= 619.

The starting material can be prepared, for example, as follows:

N-(2-Chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride
Reaction of 2,4-dichloro-8-methoxy-quinazoline (25 g) and 3-diethylaminopropylamine (18.9 ml) according to Example 56a gives N-(2-chloro-8-methoxy-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride melting at 166-172 °C. Rf(C2) 0.28.

Example 78: *trans*-Naphthalene-1-sulfonic acid {4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methyl-amide hydrochloride



A solution of 4-amino-2-chloroquinazoline (0.259 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide (0.5 g) in isopentanol (7.5 ml) is stirred at 120 °C for 19 h. After cooling to room temperature, the solvent is removed under reduced pressure. The residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid {4-[4-amino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-methyl-amide hydrochloride as a colorless amorphous solid: Rf(B2) 0.32; FAB-MS: $(M+H)^+$ = 490.

The starting material can be prepared, for example, as follows:

a) *trans*-Naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide

To a suspension of lithium aluminum hydride (4.72 g) in THF (100 ml) is added under an inert atmosphere of nitrogen a solution of *trans*-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclohexanecarboxylic acid (28.8 g) in THF (60 ml) below 10 °C. The mixture is stirred at room temperature for 1 h and is then refluxed for 15 h. After cooling to 0 °C, a mixture of THF (100 ml) and water (10 ml) is added followed by aqueous 1N NaOH solution (15 ml) and the resulting suspension is stirred at room temperature for 2 h. After the addition of magnesium sulfate (40 g) and Celite (20 g) the inorganic salts are removed by filtration. The filtrate is concentrated and the crude product is purified by recrystallization from THF-isopropyl ether to give *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide as white crystals, melting at 134-145 °C: Rf(A1) 0.25.

b) *trans*-Naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide

To a stirred suspension of *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-amide (10 g) in dichloromethane (80 ml) is added 3,4-dihydro-2H-pyran (2.85 ml) and p-toluene sulfonic acid monohydrate (57 mg) at room temperature. After stirring at room temperature for 30 min, potassium carbonate (5 g) is added and the resulting suspension is stirred for 5 min. The reaction mixture is diluted with dichloromethane (150 ml), washed with water and brine, dried over sodium sulfate and

concentrated *in vacuo*. The crude product is purified by recrystallization from ether-hexane to obtain *trans*-naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide as white crystals melting at 126-127 °C: Rf (A1) 0.64.

c) *trans*-Naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide

To a stirred solution of *trans*-naphthalene-1-sulfonic acid [4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide (11.0 g) in DMF (60 ml) is added sodium hydride (1.26 g, ca 60 %) at room temperature over a period of 5 min. After stirring at room temperature for 40 min, methyl iodide (1.97 ml) is added in a dropwise manner over 10 min. The reaction mixture is stirred at room temperature for 1 h and then concentrated under reduced pressure. The residue is partitioned between water and ethyl acetate and extracted with ethyl acetate. The combined extracts are washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. Recrystallization from ether-hexane gives *trans*-naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide as colorless crystals melting at 91-91 °C: Rf(A3) 0.29.

d) *trans*-Naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-methyl-amide

To a stirred suspension of *trans*-naphthalene-1-sulfonic acid methyl-[4-(tetrahydro-pyran-2-yloxymethyl)-cyclohexylmethyl]-amide (10.0 g) in a mixture of methanol (80 ml) and THF (40 ml) is added p-toluene sulfonic acid monohydrate (0.13 g) at room temperature. After stirring at room temperature for 26 h, potassium carbonate (5 g) is added and the resulting mixture is stirred for 10 min. The inorganic salts are filtered off and the filtrate is concentrated *in vacuo*. The residue is dissolved in ethyl acetate, washed with water and brine, dried over sodium sulfate and concentrated under reduced pressure. Recrystallization from THF-hexane yields *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cyclohexylmethyl)-methyl-amide as colorless crystals melting at 124-125 °C: Rf(A1) 0.28.

e) *trans*-Toluene-4-sulfonic acid 4-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-cyclohexylmethyl ester

To a stirred solution of *trans*-naphthalene-1-sulfonic acid (4-hydroxymethyl-cycloexylethyl)-methyl-amide (7.6 g) in dichloromethane (100 ml) is added triethyl amine (5.63 ml). To the

mixture is added p-toluene sulfonyl chloride (4.8 g) and 4-diethylamino-pyridine (0.27 g) at room temperature. The resulting mixture is stirred at room temperature for 6 h and then, is poured into water. The mixture is extracted with dichloromethane. The extract is washed with 1N HCl and aqueous saturated sodium hydrogen carbonate solution and brine. After drying over sodium sulfate, the solvent is removed under reduced pressure to give *trans*-toluene-4-sulfonic acid 4-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-cyclohexylmethyl ester as an oil: Rf(A1) 0.57.

f) *trans*-Naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)-methyl-amide
To a solution of *trans*-toluene-4-sulfonic acid 4-{[methyl-(naphthalene-1-sulfonyl)-amino]-methyl}-cyclohexylmethyl ester (10.9 g) in DMF (100 ml) is added sodium azide (4.94 g) at room temperature. The mixture is stirred at 60°C for 15 h. After cooling to room temperature, DMF is removed under reduced pressure. To the residue is added 150 ml of water and the mixture is extracted with ethyl acetate. The extract is washed with brine and is dried over sodium sulfate. The solvent is removed under reduced pressure. The residue is purified by flash column chromatography on silica gel (hexane-ethyl acetate = 4/1) to give *trans*-naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)-methyl-amide as an oil: Rf (A3) 0.33; FAB-MS $(M+H)^+$ = 373.

g) *trans*-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide
To a solution of *trans*-naphthalene-1-sulfonic acid (4-azide-methyl-cyclohexylmethyl)--methyl-amide (2.5 g) in ethyl acetate (75 ml) is added platinum(IV)-oxide (0.25 g) and the mixture is stirred under an atmosphere of hydrogen at room temperature for 35 min. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. The crude product is purified by recrystallization from ether-hexane to give *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide as colorless crystals melting at 84-86 °C: Rf(B4) 0.16.

Example 79: *trans*-Naphthalene-1-sulfonic acid methyl-{4-[4-phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride
According to the procedure described in Example 78, 2-chloro-4-phenylamino-quinazoline (0.369 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexylmethyl)-methyl-amide (0.5 g) are reacted together to give *trans*-naphthalene-1-sulfonic acid methyl-{4-[4-

phenylamino-quinazolin-2-ylamino)-methyl]-cyclohexylmethyl}-amide hydrochloride as a colorless amorphous solid: Rf(B2) 0.36; FAB-MS: $(M+H)^+$ = 566

Example 80: *trans*-Naphthalene-1-sulfonic acid {4-[1-(4-amino-quinazolin-2-ylamino)-1-methyl-ethyl]cyclohexylmethyl}-amide hydrochloride

A solution of 4-amino-2-chloroquinazoline (0.249g) and *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide (0.5 g) in iso-pentanol (7.5 ml) is stirred at 120 °C for 11 days. After removal of the solvent the residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid {4-[1-(4-amino-quinazolin-2-ylamino)-1-methyl-ethyl]cyclohexylmethyl}-amide hydrochloride as an amorphous solid: Rf(B2) 0.21; FAB-MS: $(M+H)^+$ = 504.

The starting material can be prepared, for example, as follows:

a) *trans*-Naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide

To a stirred suspension of *trans*-4-[(1-naphthalenesulfonyl)-aminomethyl]-cyclo-hexanecarboxylic acid amide (20 g) in toluene (225 ml) is added thionyl chloride (6.28 ml) at room temperature and the reaction mixture is stirred at 80°C for 8 h. The reaction mixture is poured into ice-water (300 ml) and the solution is made alkaline with 4N aqueous NaOH (50 ml) before it is extracted with ethyl acetate. The combined extracts are washed with 1% aqueous sodium carbonate solution and water, dried over sodium sulfate, and concentrated *in vacuo*. The residue is purified by recrystallization from isopropanol to give *trans*-naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide as colorless crystals, melting at 146-148 °C: Rf(A1) 0.56.

b) *trans*-Naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide

To a stirred suspension of anhydrous cesium trichloride (14.99 g) in THF (125 ml) is added a solution of methyl lithium - lithium bromide complex in diethyl ether (40 ml) below -65 °C. After stirring at -78 °C for 30 min, a solution of *trans*-naphthalene-1-sulfonic acid (4-cyano-cyclohexylmethyl)-amide (5 g) in THF is added to the mixture in a dropwise manner. The mixture is stirred at -78 °C for 5 h and at -40 °C for 16 h. Upon completion, the reaction mixture is quenched with 28% aqueous ammonia (30 ml) and the mixture is allowed to warm to room temperature and is then filtered through Celite. The filtrate is washed with

water, dried over sodium sulfate, and concentrated under reduced pressure. The residue is purified by flash chromatography to give *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide as a powder: FAB-MS:$(M+H)^+$= 361.

Example 81: *trans*-Naphthalene-1-sulfonic acid {4-[1-methyl-1-(4-phenylamino-quinazolin-2-ylamino)-ethyl]-cyclohexylmethyl}-amide hydrochloride

According to the procedure described in Example 80, 2-chloro-4-phenylamino-quinazoline (0.33 g) and *trans*-naphthalene-1-sulfonic acid [4-(1-amino-methyl-ethyl)-cyclohexylmethyl]-amide (0.465 g) are reacted together to give *trans*-naphthalene-1-sulfonic acid {4-[1-methyl-1-(4-phenylamino-quinazolin-2-ylamino)-ethyl]-cyclohexylmethyl}-amide hydrochloride as an amorphous solid: Rf (B2) 0.35; FAB-MS: $(M+H)^+$= 580.

Example 82: *trans* Naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride

A suspension of 4-amino-2-chloro-quinazoline (0.359 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentyl alcohol (4 ml) is stirred at 120 °C for 21 h. The cooled reaction mixture is concentrated *in vacuo* to give a solid which is triturated with dioxane, filtered and then dried overnight under high vacuum to give *trans* naphthalene-2-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride as an amorphous solid melting at 209-212 °C. Rf(C5) 0.47; ESI-MS: $(M+H)^+$=462.

The starting material can be prepared, for example, as follows:

a) *trans*-[4-(Naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of naphthalene-2-sulfonyl chloride (5.12 g) in N,N-dimethylformamide (30 ml) is added dropwise to a milky solution of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5.08 g) (Example 58b) and ethyldiisopropylamine (4.7 ml) in N,N-dimethylformamide (100 ml) at 0°C. The reaction is stirred at room temperature for 5.5 h and then concentrated *in vacuo*. The residue is taken up in dichloromethane and washed with 0.5N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B1) yields *trans*-[4-

(naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a tan foam. Rf(B1) 0.40; ESI-MS: $(M-H)^-$=417.

b) *trans*-Naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide

A solution of 4N HCl in dioxane (50 ml) is added dropwise over 20 min to a yellow solution of *trans*-[4-(naphthalene-2-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (8.43 g) in dichloromethane (50 ml) at 0 °C. Methanol (10 ml) and additional 4N HCl in dioxane (35 ml) are added after 6 h. The reaction mixture is worked up after 21 h by concentrating *in vacuo*. The residue is taken up in 1N aqueous NaOH and extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to give an oil. Dilution with hexanes followed by cooling (-20 °C) overnight and then filtration gives *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide as a solid. Rf(C2) 0.11; ESI-MS: $(M+H)^+$=319.

In analogous manner as described hereinbefore following compound can be prepared:

Example 83: *trans* Naphthalene-2-sulfonic acid (4-{[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl}-cyclohexyl)-amide hydrochloride

Rf(C5) 0.57; ESI-MS: $(M+H)^+$=572, 574.

Example 84: *trans* Naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide

A suspension of 4-amino-2-chloro-quinazoline (0.359 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) isopentanol (4 ml) is stirred at 120 °C for 21 h. The cooled reaction mixture is concentrated *in vacuo* to give an oily residue. Chromatography on silica gel (B7) gives *trans* naphthalene-1-sulfonic acid {4-[(4-amino-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide as a solid. Rf(C5) 0.43; ESI-MS: $(M+H)^+$=462.

The starting material can be prepared, for example, as follows:

a) *trans*-[4-(Naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of naphthalene-1-sulfonyl chloride (5.18 g) in N,N-dimethylformamide (30 ml) is added dropwise to a milky solution of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5.05 g) and ethyldiisopropylamine (4.7 ml) in N,N-dimethylformamide (100 ml) at 0°C. The reaction is stirred at room temperature for 5 h and then concentrated *in vacuo*. The residue is taken up in dichloromethane and washed with 0.5N aqueous HCl, saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and concentrated. The residue is diluted with ethyl acetate, filtered and washed with hexanes to give *trans*-[4-(naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a white powder. Rf(B1) 0.39; ESI-MS: (M-H)=417.

b) *trans*-Naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide

A solution of 4N HCl in dioxane (50 ml) is added dropwise over 20 min to a yellow solution of *trans*-[4-(naphthalene-1-sulfonylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (7.90 g) in dichloromethane (45 ml) at 0 °C. Methanol (10 ml) and additional 4N HCl in dioxane (35 ml) are added after 6 h. The reaction mixture is worked up after 21 h by concentrating *in vacuo*. The residue is taken up in 1N aqueous NaOH and extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated to give an oil. Dilution with hexanes followed by cooling (-20 °C) overnight and then filtration gives *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide as a solid. Rf(C2) 0.08; ESI-MS: $(M+H)^+$=319.

Example 85: *trans*-Naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide

A suspension of 4-amino-2-chloro-8-methoxy-quinazoline (0.419 g) and *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentanol (4 ml) is stirred at 120 °C for 47 h. The cooled reaction mixture is concentrated *in vacuo* to give an oily residue. Dichloromethane and 1N aqueous NaOH are added, and the mixture is stirred at room temperature for 19 h. The suspension is filtered and the phases separated. The aqueous phase is re-extracted with dichloromethane. The combined organic layers are dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel (B6-B8) to give *trans* naphthalene-2-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-yl-amino)-methyl]-cyclohexyl}-amide as a beige solid melting at 202-205 °C. Rf(C5) 0.32; ESI-MS: $(M+H)^+$=492.

In analogous manner as described hereinbefore following compound can be prepared:

Example 86: *trans*-Naphthalene-1-sulfonic acid (4-{[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-methyl}-cyclohexyl)-amide

Rf(C5) 0.52; ESI-MS: $(M+H)^+$=572, 574.

Example 87: *trans*-Naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride

A suspension of 4-amino-2-chloro-8-methoxy-quinazoline (0.419 g) and *trans*-naphthalene-1-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.637 g) in isopentyl alcohol (4 ml) is stirred at 120 °C for 47 h. The cooled reaction mixture is concentrated *in vacuo* to give a solid which is triturated with dioxane. The suspension is filtered, the filtrate re-concentrated and the resulting residue chromatographed on silica gel (B2-B8) to give *trans* naphthalene-1-sulfonic acid {4-[(4-amino-8-methoxy-quinazolin-2-ylamino) methyl]-cyclohexyl}-amide hydrochloride as a light yellow solid. Rf(C5) 0.28; ESI-MS: $(M+H)^+$=492.

Example 88: *trans* Naphthalene-2-sulfonic acid (4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexyl)-amide

A suspension of N-(2-chloro-quinazolin-4-yl)-N',N'-dimethyl-ethane-1,2-diamine (0.574 g), *trans*-naphthalene-2-sulfonic acid (4-aminomethyl-cyclohexyl)-amide (0.764 g), ethyldiisopropylamine (1.02 ml) and phenol (2.82 g) is stirred at 150°C for 8 h. The cooled reaction mixture is diluted with dichloromethane and 1N aqueous NaOH and the phases separated. The aqueous phase is re-extracted with dichloromethane and the combined organic layers are washed with brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B6-B8) gives *trans* naphthalene-2-sulfonic acid (4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexyl)-amide as a light yellow foam. Rf(C5) 0.28; ESI-MS: $(M+H)^+$=533.

In analogous manner as described hereinbefore following compound can be prepared:

Example 89: *trans* Naphthalene-1-sulfonic acid (4-{[4-(2-dimethylamino-ethylamino)-quinazolin-2-ylamino]-methyl}-cyclohexyl)-amide

Rf(C5) 0.14; ESI-MS: $(M+H)^+$=533.

Example 90: *trans*-N-{4-[(4-Phenylamino-quinazolin-2-ylamino)]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide hydrochloride

A solution of *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride (0.35 g) and diisopropylethylamine (0.7 ml) in dichloromethane (10 ml) is cooled to 0 °C and treated with dimethylsulfamoyl chloride (0.3 ml). After stirring at room temperature for 20 h, the reaction mixture is concentrated and the residue is triturated with aqueous sodium hydrogen carbonate, filtered and the dried residue is chromatographed (silica gel, B1) to give the product as an oil. It is taken up in methanol and treated at 0 °C with 4N HCl in dioxane. Concentration in vacuo followed by crystallization from isopropanol and diethyl ether yields *trans*-N-{4-[(4-phenylamino-quinazolin-2-ylamino)]-cyclohexylmethyl}-(N,N-dimethylamino)-sulfonamide hydrochloride as white crystals melting at 230-234 °C. Rf(D1) 0.37; FAB-MS: $(M+H)^+$= 455.

The starting material can be prepared, for example, as follows:

a) *trans*-[4-(*tert.*-Butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester
To a stirred suspension of *trans*-4-(*tert.*-butoxycarbonylaminomethyl)-cyclohexanecarboxylic acid (obtained according to: FR 2,701,480) (45 g) and diphenylphosphoryl azide (44 ml) in toluene (600 ml) is added triethylamine (32 ml) below 0 °C over a period of 20 min. The mixture is slowly warmed up and stirred at 70 °C for 4 h. After cooling to 40 °C, benzyl alcohol (36 ml) is added and the reaction mixture is heated at reflux for 20 h. The cold reaction mixture is washed with water and brine and dried over magnesium sulfate. Concentration in vacuo followed by crystallization from ethyl acetate and diethyl ether yields *trans*-[4-(*tert.*-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester as colorless crystals, melting at 126 - 129 °C. Rf(A7) 0.47.

b) *trans*-(4-Amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester

A solution of [4-(tert.-butoxycarbonylaminomethyl)-cyclohexyl]-carbamic acid benzylester (4 g) in methanol (200 ml) is hydrogenated in the presence of palladium on charcoal 10% (0.7 g) at ambient temperature and pressure. The catalyst is removed by filtration and the filtrate is concentrated in vacuo to yield and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester as a colorless oil, Rf(D1) 0.12.

c) *trans*-[4-(4-Phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester hydrochloride

A solution of 2-chloro-4-phenylamino-quinazoline (9.72 g) and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid tert.-butyl ester (10.1 g) in isopentylalcohol (150 ml) is stirred at 120 °C for 20 h. The reaction mixture is cooled to ambient temperature and the product is collected by suction filtration. Crystallization from isopropanol yields *trans*-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester hydrochloride as a colorless crystals melting at 161 - 163 °C; Rf(D1) 0.44.

d) *trans*-4-(Aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride

A suspension of *trans*-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester hydrochloride (6.8 g) in chloroform (50 ml) is treated with a 4 N HCl solution in dioxane (20 ml) at 0 °C. After completion, the reaction mixture is concentrated in vacuo and the residue is recrystallized from isopropanol to yield *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline dihydrochloride as white crystals melting at 326 - 330 °C. The dihydrochloride salt is taken up in a saturated aqueous potassium carbonate solution and dichloromethane. After extraction with ethyl acetate, the combined phases are dried over sodium sulfate and concentrated to give *trans*-4-(aminomethyl-cyclohexylamino)-4-phenylamino-quinazoline as a light yellow oil. Rf(G1) 0.04. FAB-MS: $(M+H)^+$ = 348.

Example 91: *trans*-N-(4-{[4-(4-Chloro-phenyl)amino]-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide hydrochloride

According to the procedure described in Example 90, *trans*-4-(aminomethyl-cyclohexylamino)-4-(4-chloro-phenyl)amino-quinazoline dihydrochloride (0.36 g), diisopropylethylamine (0.6 ml) and dimethylsulfamoyl chloride (0.2 ml) are reacted together to give *trans*-N-(4-{[4-(4-chloro-phenyl)amino}-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-di-

methylamino)-sulfonamide hydrochloride as a white powder melting at 206-212 °C: Rf(H1) 0.44, ESI-MS: $(M+H)^+$=489.

In analogous manner as described hereinbefore following compound can be prepared:

Example 92: *trans*-N-{4-[[4-(4-Fluoro-phenyl)amino]-8-methoxy-quinazolin-2-ylamino}-cyclohexylmethyl)-(N,N-dimethylamino)-sulfonamide hydrochloride

167-169 °C: Rf(H1) 0.46, FAB-MS: $(M+H)^+$=503.

Example 93: *trans*-N-{4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino}-cyclohexylmethyl)-methanesulfonamide hydrochloride

258-262 °C. Rf(D1) 0.35.

Example 94: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester

According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (8.7 g), diisopropylethylamine (6 ml) and *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (8.4 g) are reacted together to give *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester as white crystals melting at 235-238 °C. Rf(H1) 0.42.

In analogous manner as described hereinbefore following compound can be prepared:

Example 95: *trans*-{4-[4-(Cyclopropylamino)-8-methoxy-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester

224-227 °C. Rf(H1) 0.46.

Example 96: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-acetamide hydrochloride

A solution of *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenyl)-quinazoline-2,4-diamine dihydrochloride (0.955 g) and diisopropylethylamine (1 ml) in 25 ml of dichloromethane is cooled to 0 °C and treated with acetic anhydride (0.28 ml). After stirring for 1 h at room temperature, the reaction mixture is diluted with aqueous potassium carbonate and extracted with dichloromethane. The combined extracts are dried and concentrated *in vacuo*. The residue is taken up in methanol and treated at 0 °C with a 4 N HCl in dioxane. Concentration in vacuo followed by crystallization from ethanol and acetonitrile yields *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-acetamide hydrochloride as white crystals melting at 300-304 °C. Rf(H1) 0.32.

The starting material can be prepared, for example, as follows:

trans-4-(Aminomethyl-cyclohexyl)-4-(4-chloro-phenyl-quinazolin-2,4-diamine dihydrochloride

According to the procedure described in Example 90b *trans*-{4-[4-(4-chloro-phenylamino)-quinazoline-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester hydrochloride (2.44 g) and 5N HCl solution in isopropanol (20 ml) are reacted together to give *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenylamino)-quinazoline-2,4-diamine dihydrochloride as an amorphous solid: Rf(H1) 0.14, ESI-MS: $(M+H)^+$ = 382, 384.

Example 97: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-benzamide hydrochloride

According to the procedure described in Example 94 *trans*-(4-aminomethyl-cyclohexyl)-4-(4-chloro-phenylamino)-quinazoline-2,4-diamine dihydrochloride (0.32 g), diisopropyl-ethylamine (0.26 g) and benzoic anhydride (0.26 g) are reacted together to give *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-benzamide hydrochloride as white crystals melting at 245-248 °C. Rf(H1) 0.23, ESI-MS: $(M+H)^+$ = 486, 488.

Example 98: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide hydrochloride

According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (0.725 g), diisopropylethylamine (0.51 ml) and *trans*-(4-amino-cyclo-hexylmethyl)-2-methoxy-benzamide (0.656 g) are reacted together to give *trans*-{4-[4-(4-

chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide hydrochloride as light yellow crystals melting at 242-245 °C: Rf(H1) 0.43, ESI-MS: $(M+H)^+$ = 516, 418.

The starting material can be prepared, for example, as follows:

a) *trans*-(-Aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride
According to the procedure described in Example 90b, *trans*-[4-(*tert.*-butoxycarbonyl-aminomethyl)-cyclohexyl]-carbamic acid benzylester (49 g) and 4N HCl solution in dioxane (20 ml) are reacted together to give *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride as white crystals melting at 194-197 °C: Rf(G1) 0.10.

b) {4-[(2-Methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester
According to the procedure described in Example 93, *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride (6.0 g), diisopropylethylamine (8.5 ml) and 2-methoxy-benzoylchloride (2.7 ml) are reacted together to give {4-[(2-methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester as white crystals melting at 150-152 °C: Rf(A7) 0.30.

c) *trans*-4-(Amino-cyclohexylmethyl)-2-methoxy-benzamide
A suspension of {4-[(2-methoxy-benzoylamino)-methyl]-cyclohexyl}-carbamic acid benzylester (5.75 g) and 10% Pd/C (0.5 g) in methanol (300 ml) is hydrogenated under atmospheric pressure at room temperature for 6 h. The catalyst is filtered off over Celite and the filtrate is concentrated *in vacuo* to give *trans*-4-(amino-cyclohexylmethyl)-2-methoxy-benzamide as white crystals melting at 59-61 °C: Rf(G1) 0.06.

In analogous manner as described hereinbefore following compound can be prepared:

Example 99: N-*trans*-{4-[4-(Cyclopropylmethylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-2-methoxy-benzamide hydrochloride

182-184 °C, Rf(H1) 0.41, ESI-MS: $(M+H)^+$ = 460.

Example 100: *trans*-4-(4-Chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine

To a suspension of lithium aluminum hydride (2.5 g) in THF is added under an inert atmosphere of nitrogen a solution of *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester (2.41 g) in THF (60 ml) below 10 °C. The mixture is heated at reflux for 5 h. After cooling to 0 °C, a mixture of THF and water is added followed by aqueous 4N NaOH solution and water. The resulting suspension is stirred for 1 h at room temperature. After the addition of magnesium sulfate and Celite the inorganic salts are removed by filtration. The filtrate is concentrated and the crude product is purified by chromatography (silica gel, B2-B5) to give *trans*-4-(4-chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine as an amorphous solid: Rf(D2) 0.36, ESI-MS: $(M+H)^+$ = 396, 398.

Example 101: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide

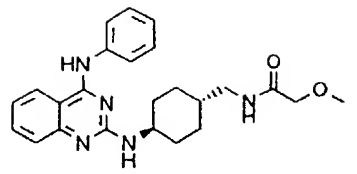
According to the procedure described in Example 96, *trans*-4-(4-chloro-phenylamino)-2-(4-methylaminomethyl-cyclohexyl)-quinazoline-2,4-diamine (0.2 g), diisopropylethylamine (0.12 g) and acetic anhydride (0.06 g) are reacted together to yield *trans*-{4-[4-(4-chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-acetamide as an amorphous solid: Rf(D1) 0.43, ESI-MS: $(M+H)^+$ = 438, 440.

In analogous manner as described hereinbefore following compound can be prepared:

Example 102: *trans*-{4-[4-(4-Chloro-phenylamino)-quinazolin-2-ylamino]-cyclohexylmethyl}-N-methyl-benzamide

157-160 °C, Rf(H1) 0.46, ESI-MS: $(M+H)^+$ = 500, 502.

Example 103: *trans*-2-Methoxy-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide



According to the procedure described in Example 78, 2-chloro-4-(4-chloro-phenyl)-amino-quinazoline (2.6 g) and *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide (2 g) are reacted together to give *trans*-2-methoxy-[4-(4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide as white crystals melting at 204-210 °C: Rf(H1) 0.46, ESI-MS: $(M+H)^+$ = 420.

The starting material can be prepared, for example, as follows:

a) *trans*-{4-[(2-Methoxy-acetylamino)-methyl]-cyclohexyl}-carbamic acid benzylester
According to the procedure described in Example 98b, *trans*-(-aminomethyl-cyclohexyl)-carbamic acid benzylester hydrochloride (Example 98a) (8.0 g), diisopropylethylamine (12 ml) and methoxy-acetylchloride (2.7 ml) are reacted together to give *trans*-{4-[(2-methoxy-acetylamino)-methyl]-cyclohexyl}-carbamic acid benzylester as white crystals melting at 167-169 °C: Rf(H1) 0.45, ESI-MS: $(M+H)^+$ = 335.

b) *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide
According to the procedure described in Example 98c, *trans*-{4-[(2-methoxy-acetylamino)-methyl]-cyclohexyl}-carbamic acid benzylester (5.75 g) and 10% Pd/C (0.5 g) are hydrogenated to give *trans*-(4-amino-cyclohexylmethyl)-2-methoxy-acetamide as a light yellow waxy solid: Rf(D2) 0.31, ESI-MS: $(M+H)^+$ = 201.

In analogous manner as described hereinbefore following compounds can be prepared:

Example 104: *trans*-2-Methoxy-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-acetamide hydrochloride

149-152 °C, Rf(H1) 0.41.

Example 105: *trans*-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester hydrochloride

207-210 °C, Rf(D2) 0.34, FAB-MS: $(M+H)^+$ = 478.

Example 106: *trans*-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-methanesulfonamide hydrochloride

177-182 °C, FAB-MS: $(M+H)^+$ = 456.

Example 107: *trans*-[4-(8-methoxy-4-phenylamino-quinazolin-2-ylamino)-cyclohexylmethyl]-(N,N-dimethylamino)-sulfonamide hydrochloride

258-261 °C, Rf(H1) 0.42, FAB-MS: $(M+H)^+$ = 485.

Example 108: *trans*-4-(Cyclopropylmethyl)-2-(4-piperidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride
Rf(D2) 0.13.

Example 109: *trans*-4-(4-Chloro-phenyl)-2-(4-piperidin-1-ylmethyl-cyclohexyl)-quinazoline-2,4-diamine dihydrochloride

Rf(D2) 0.12.

Example 110: 4-(3-Chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine hydrochloride
According to the procedure described in Example 78, 2-chloro-4-(3-chloro-phenyl)-amino-quinazoline (0.435 g) and cyclohexylamine (0.17) are reacted together to give 4-(3-chloro-phenyl)-2-cyclohexyl-quinazoline-2,4-diamine hydrochloride as a white powder melting at 237-240 °C: Rf(H1) 0.56.

In analogous manner as described hereinbefore following compounds can be prepared:

Example 111: 2-(N-Methyl-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

M.p. 269 - 270 °C.

Example 112: 2-(N-Methyl-cyclohexylamino)-8-hydroxy-4-phenylamino-quinazoline hydrochloride

Rf(A1) 0.82.

Example 113: 2-(N-Methyl-cyclohexylamino)-8-methoxy-4-phenylamino-quinazoline hydrochloride

Rf(A1) 0.46.

Example 114: 2-(N-Methyl-cyclohexylamino)-8-(methoxycarbonyl-methoxy)-4-phenylamino-quinazoline hydrochloride

M.p. 192 - 193 °C.

Example 115: 2-(N-Methyl-cyclohexylamino)-8-[(2-hydroxy-ethoxy)]-4-phenylamino-quinazoline hydrochloride

M.p. 232 - 234 °C.

Example 116: 2-(N-Methyl-cyclohexylamino)-8-hydroxy-4-(4-fluoro-phenylamino)-quinazoline hydrochloride

M.p. 285 - 286 °C.

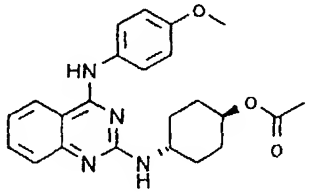
Example 117: 2-(N-Ethyl-cyclohexylamino)-8-hydroxy-4-(4-chloro-phenylamino)-quinazoline hydrochloride

Rf(A1) 0.91.

Example 118: *trans*-2-(4-Benzoyloxy-cyclohexylamino)-4-phenylamino-quinazoline hydrochloride

M.p. 238 - 239 °C.

Example 119: *trans*-2-(4-Acetoxy-cyclohexylamino)-4-(4-methoxy-phenylamino)-quinazoline hydrochloride



M.p. 168 - 169 °C.

Example 120: N(2)-(*trans*-4-Dimethylamino-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine

According to the procedure described in Example 78, *trans*-(4-aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid) (0.556 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.286 g) and ethyldiisopropylamine (0.36 ml) are reacted together to give N(2)-(*trans*-4-dimethylamino-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a foam melting at 97-103 °C. Rf(C3) 0.15; ESI-MS: $(M+H)^+$=404.

The starting material can be prepared, for example, as follows:

a) 4-Amino-4'-methyl-biphenyl-3-carboxylic acid

A solution of cesium carbonate (127.3 g) in degassed water (145 ml) is added to a suspension of 2-amino-5-bromo-benzoic acid (60 g) in toluene (1000 ml) at room temperature under an inert atmosphere of argon. *p*-Tolylboronic acid (49.1 g) and tetrakis(triphenylphosphine)palladium(0) (4.5 g) are added and the mixture is heated at reflux for 18 h. Water is added (500 ml) to the cooled reaction mixture and the organic phase is extracted with water. The combined aqueous phases are treated with activated charcoal and filtered through Celite. The filtrate is acidified with 4N HCl and the resulting suspension is extracted with ethyl acetate. The combined organic extracts are washed with brine, dried over magnesium sulfate, treated with activated charcoal, filtered, and

concentrated to ca. 400 ml. The resulting crystals are filtered and dried to give 4-amino-4'-methyl-biphenyl-3-carboxylic acid. Rf(B2) 0.62.

b) 6-*p*-Tolyl-quinazoline-2,4-diol

According to the procedure described in Example 127a, 4-amino-4'-methyl-biphenyl-3-carboxylic acid (36.4 g) is converted into 6-*p*-tolyl-quinazoline-2,4-diol. Rf(B2) 0.70; ESI-MS: $(M+H)^+$=253.

c) 2,4-Dichloro-6-*p*-tolyl-quinazoline

According to the procedure described in Example 127b, 6-*p*-tolyl-quinazoline-2,4-diol (37.8 g) is converted into 2,4-dichloro-6-*p*-tolyl-quinazoline melting at 122-124 °C. Rf(A11) 0.27.

d) (2-Chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine

According to the procedure described in Example 40a, 2,4-dichloro-6-*p*-tolyl-quinazoline (9.1 g) and methylamine (10 ml) in ethanol (100 ml) are reacted together to give (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine as white crystals melting at 277-278 °C. Rf(B2) 0.22; ESI-MS: $(M+H)^+$=284,286.

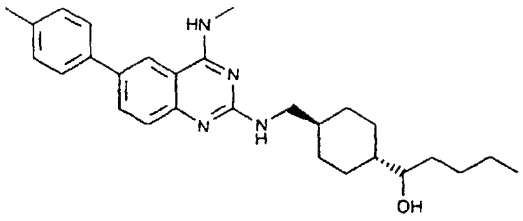
e) *trans*-(4-Dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A mixture of *trans*-(4-amino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (Example 90b) (1.05 g), 36.5% aqueous formaldehyde (0.8 ml) and 10% Pd/C (200 mg) in methanol (25 ml) and water (5 ml) is hydrogenated under 1 atmosphere of hydrogen. After 4 h, the catalyst is filtered off and the filtrate concentrated to give *trans*-(4-dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a pale yellow oil which solidified on standing. Rf(D1) 0.23; ESI-MS: (M+H)=257.

f) *trans*-(4-Aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid)

Reaction of *trans*-(4-dimethylamino-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.11 g) and trifluoroacetic acid (5 ml) gives the *trans*-(4-aminomethyl-cyclohexyl)-dimethyl-amine bis(trifluoroacetic acid) salt, which is used without further purification.

Example 121: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol



According to the proceduredescribed in Example 78, 1-(*trans*-4-aminomethyl-cyclohexyl)-pentan-1-ol (0.199 g) and (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.284 g) are reacted together to give 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol as a foam: Rf(C5) 0.43; ESI-MS: $(M+H)^+$=447.

The starting materials can be prepared, for example, as follows:

a) *trans*-(4-Formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A mixture of "wet" dichloromethane (100 ml, containing 0.41 ml of water) is added over 20 min to a suspension of *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (5 g) (Example 11a) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (13.1 g) in dichloromethane (50 ml) at room temperature. After 15 min, the reaction mixture is diluted with diethylether, washed with 1:1 10% aqueous sodium thiosulfate/saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated to give *trans*-(4-formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a light yellow oil which is used without further purification. Rf(A1) 0.57.

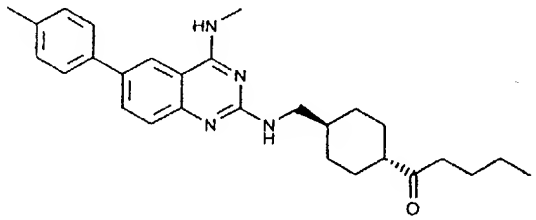
b) [*trans*-4-(1-Hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester

A solution of *trans*-(4-formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (4.95 g) in THF (40 ml) is added dropwise to a 0.7M solution of butylmagnesium chloride in THF (60 ml) at -78 °C. Additional THF (70 ml) is added to aid stirring. After 1 h, the reaction mixture is quenched with saturated aqueous ammonium chloride, diluted with water and extracted with ethyl acetate. The combined organic phases are dried over magnesium sulfate and concentrated. Chromatography on silica gel (A4 then A1) yields [*trans*-4-(1-hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester as a white solid. Rf(A1) 0.60; ESI-MS: $(M+H)^+$=300.

c) 1-(*trans*-4-Aminomethyl-cyclohexyl)-pentan-1-ol

Reaction of [*trans*-4-(1-hydroxy-pentyl)-cyclohexylmethyl]-carbamic acid *tert*-butyl ester (3.02 g) and trifluoroacetic acid (25 ml) according to the procedure described in Example 120f gives the crude trifluoroacetic acid salt. The residue is dissolved in dichloromethane and washed with 1N NaOH. The aqueous phase is saturated with sodium chloride and extracted with dichloromethane. The combined organic phases are washed with brine, dried over magnesium sulfate and concentrated to give 1-(*trans*-4-aminomethyl-cyclohexyl)-pentan-1-ol, which is used without further purification. Rf(C5) 0.21; ESI-MS: $(M+H)^+$=200.

Example 122: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-one



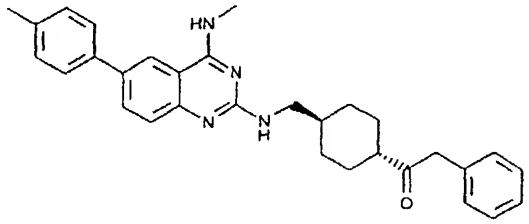
A mixture of "wet" dichloromethane (1.11 ml containing 0.003 ml of water) is added to a suspension of 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-ol (0.072 g) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (0.103 g) in dichloromethane (0.5 ml) at room temperature. After 2 h, an additional amount of Dess-Martin periodinane (0.068 g) in dichloromethane (1.5 ml) is added. After 5 h, the reaction mixture is diluted with dichloromethane, washed with 1:1 10% aqueous sodium thiosulfate/saturated aqueous sodium bicarbonate, water and brine, dried over sodium sulfate and concentrated. Chromatography on silica gel (B1 then C10) yields 1-{*trans*-4-[(4-methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-pentan-1-one as a solid melting at 193-198 °C. Rf(C5) 0.44; ESI-MS: $(M+H)^+$=445.

In analogous manner as described hereinbefore following compound can be prepared:

Example 123: {*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-phenyl-methanol

Rf(C10) 0.34; ESI-MS: $(M+H)^+$=467.

Example 124: 1-{*trans*-4-[(4-Methylamino-6-*p*-tolyl-quinazolin-2ylamino)-methyl]-cyclohexyl}-2-phenyl-ethanone



Rf(C10) 0.39; ESI-MS: $(M+H)^+$=479.

Example 125: N(2)-(*trans*-4-Ethanesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine

3-Chloroperoxybenzoic acid (0.188 g, *ca.* 55%) is added to a solution of N(2)-(*trans*-4-ethyl-sulfanylmethyl-cyclohexylmethyl)-N4-methyl-6-*p*-tolyl-quinazoline-2,4-diamine (0.1 g) in dichloromethane (4 ml) at -78 °C. After 1 h, the mixture is warmed to room temperature and stirred an additional 2 h. The reaction mixture is diluted with dichloromethane and washed with 1N NaOH and brine and the organic phase is dried over sodium sulfate and concentrated. Chromatography on silica gel (C8) yields N(2)-(*trans*-4-ethanesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a solid melting at 99-103 °C. Rf(C8) 0.37; ESI-MS: $(M+H)^+$=467.

The starting material can be prepared, for example, as follows:

a) Toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester

A solution of *p*-toluenesulfonyl chloride (20.6 g) in pyridine (50 ml) is added to a solution of *trans*-(4-hydroxymethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (Example 11a) (20 g) in pyridine (160 ml) at 0 °C, and the reaction mixture is allowed to warm to room temperature. 4Å molecular sieves are added after 22 h and the reaction is stirred a further 5 h. The mixture is filtered, concentrated and the residue is then partitioned between ethyl acetate and water. The organic phase is washed with water, 10% aqueous citric acid and brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (A9

then A10) yields toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester as a white solid. Rf(A1) 0.74.

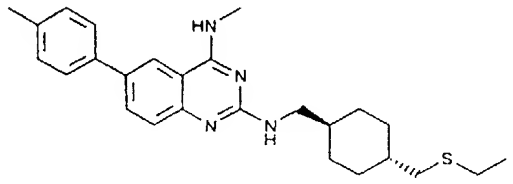
b) (*trans*-4-Ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester

A solution of toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester (10 g) in N,N-dimethylformamide (70 ml) is added to a suspension of ethanethiol sodium salt (4.68 g) in N,N-dimethylformamide (80 ml) at room temperature, and the reaction mixture is then heated to 50 °C. After 5 h, the reaction is concentrated and the residue is partitioned between ethyl acetate and water. The aqueous phase is re-extracted with ethyl acetate and the combined organic phases are washed with brine, dried over magnesium sulfate and concentrated. Chromatography on silica gel (A5) yields (*trans*-4-ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a solid. Rf(A4) 0.70; ESI-MS: $(M+H)^+$=288.

c) (*trans*-4-Ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid

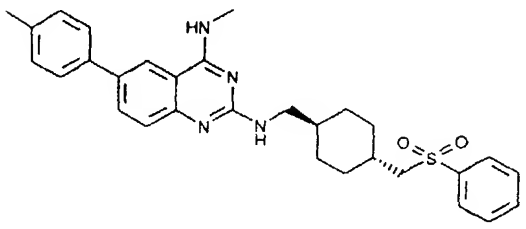
Trifluoroacetic acid (15 ml) is added dropwise to a solution of (*trans*-4-ethylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.51 g) in dichloromethane (30 ml) at 0 °C. The reaction mixture is worked up after 4.5 h by concentrating to give (*trans*-4-ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid which is used without further purification. Rf(C5) 0.42; ESI-MS: $(M+H)^+$=188.

d) N(2)-(*trans*-4-Ethylsulfanylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine



According to the procedure described in Example 78, (*trans*-4-ethylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid (0.433 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.285 g) and ethyldiisopropylamine (0.18 ml) are reacted together to give N(2)-(*trans*-4-ethylsulfanylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine as a foam: Rf(C8) 0.46; ESI-MS: $(M+H)^+$=435.

Example 126: N(2)-(*trans*-4-Benzenesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine



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According to the proceduredescribed in Example 124, N(2)-(*trans*-4-phenylsulfanylmethyl-cyclohexylmethyl)-N4-methyl-6-*p*-tolyl-quinazoline-2,4-diamine (0.1 g) and 3-Chloro-peroxybenzoic acid (0.164 g, *ca.* 55%) are reacted together to give N(2)-(*trans*-4-benzenesulfonylmethyl-cyclohexylmethyl)-N(4)-methyl-6-*p*-tolyl-quinazoline-2,4-diamine: Rf(C1) 0.16; ESI-MS: $(M+H)^+$=515.

The starting material can be prepared, for example, as follows:

a) (*trans*-4-Phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester
Reaction of toluene-4-sulfonic acid 4-*trans*-(*tert*-butoxycarbonylamino-methyl)-cyclohexylmethyl ester (10 g) and thiophenol sodium salt (7.2 g) followed by chromatography (silica gel, B10 then B9) yields (*trans*-4-phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester as a solid. Rf(A4) 0.66; ESI-MS: $(M+H)^+$=336.

b) (*trans*-4-Phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid
Reaction of (*trans*-4-phenylsulfanylmethyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (1.52 g) and trifluoroacetic acid (30 ml) gives the (*trans*-4-phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid salt, which is used without further purification. Rf(C5) 0.40; ESI-MS: $(M+H)^+$=236.

c) N(4)-Methyl-N(2)-(*trans*-4-phenylsulfanylmethyl-cyclohexylmethyl)-6-*p*-tolyl-quinazoline-2,4-diamine

According to the procedure described in Example 78, (*trans*-4-phenylsulfanylmethyl-cyclohexyl)-methylamine trifluoroacetic acid (0.351 g), (2-chloro-6-*p*-tolyl-quinazolin-4-yl)-methyl-amine (0.284 g) and ethyldiisopropylamine (0.18 ml) are reacted together to give N(4)-methyl-N(2)-(*trans*-4-phenylsulfanylmethyl-cyclohexylmethyl)-6-*p*-tolyl-quinazoline-2,4-diamine as a foam: Rf(B2) 0.42; ESI-MS: $(M+H)^+$=483.

Example 127: 1-(*trans*-4-{[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-pentan-1-ol

According to the proceduredescribed in Example 56, 1-(*trans*-4-aminomethyl-cyclohexyl)-pentan-1-ol (0.239 g), N-(2-chloro-6,8-dimethyl-quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine (0.357 g) and ethyldiisopropylamine (0.53 ml) are reacted together to give 1-(*trans*-4-{[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-pentan-1-ol: Rf(C9) 0.67; ESI-MS: $(M+H)^+$=484.

The starting material can be prepared, for example, as follows:

a) 6,8-Dimethyl-quinazoline-2,4-diol

To a suspension of 3,5-dimethylanthranilic acid (49.86 g) in dioxane (400 ml) is added acetic acid (18.7 ml) and water (300 ml) at 10 °C. A solution of potassium isocyanate (26.66 g) in water (50 ml) is added dropwise over 15 min, and the reaction mixture is stirred at room temperature for 4.5 h. NaOH pellets (160.9 g) are added all at once and the suspension is heated to reflux for 1.5 h. The reaction mixture is acidified by the dropwise addition of concentrated aqueous HCl and filtered. The solid is washed with water, triturated with acetone and methyl *tert*-butyl ether, and then dried under vacuum to give 6,8-dimethyl-quinazoline-2,4-diol as an amorphous solid. Rf(A4) 0.09; ESI-MS: $(M-H)^-$=189.

b) 2,4-Dichloro-6,8-dimethyl-quinazoline

To a mixture of phosphorus oxychloride (115 ml) and phosphorus pentachloride (23 g) are added 6,8-dimethyl-quinazoline-2,4-diol (25 g) at room temperature. The resulting suspension is heated under reflux for 14 h, cooled to room temperature, diluted with toluene (700 ml) and then poured into water. The mixture is stirred for 20 min, filtered and then the

liquid phases are separated. The organic phase is washed with water , 1N aqueous sodium carbonate and brine, dried over magnesium sulfate and concentrated in vacuo to give 2,4-dichloro-6,8-dimethyl-quinazoline as a solid melting at 140-143 °C. Rf(A4) 0.72.

c) N-(2-Chloro-6,8-dimethyl--quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride

The reaction of 2,4-dichloro-6,8-dimethyl-quinazoline (2.79 g) and 3-diethylamino-propylamine according to the procedure described in Example 56a gives N-(2-chloro-6,8-dimethyl--quinazolin-4-yl)-N',N'-diethyl-propane-1,3-diamine hydrochloride as a solid melting at 159-161 °C. Rf(C8) 0.30; ESI-MS: $(M+H)^+$=321, 323.

Example 128: 1-(*trans*-4-{[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-pentan-1-one

According to the proceduredescribed in Example 122, 1-(*trans*-4-{[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-pentan-1-ol (0.094 g) and 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (0.201 g) are reacted together to give 1-(*trans*-4-{[4-(3-diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-pentan-1-one: Rf(C5) 0.27; ESI-MS: $(M+H)^+$=482.

Example 129: 1-(*trans*-4-{[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-2-phenyl-ethanone

Rf(C10) 0.31; ESI-MS: $(M+H)^+$=516.

In analogous manner as described hereinbefore following compound can be prepared:

Example 130: (*trans*-4-{[4-(3-Diethylamino-propylamino)-6,8-dimethyl-quinazolin-2ylamino]-methyl}-cyclohexyl)-phenyl-methanone

Rf(C10) 0.35; ESI-MS: $(M+H)^+$=502.

Example 131:

Tablets, each containing 50 mg of active ingredient, for example, 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 10,000 tablets)

Active ingredient	500.0 g
Lactose	500.0 g
Potato starch	352.0 g
Gelatin	8.0 g
Talc	60.0 g
Magnesium stearate	10.0 g
Silica (highly disperse)	20.0 g
Ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, and the mixture is moistened using an alcoholic solution of the gelatin and granulated by means of a sieve. After drying, the remainder of the potato starch, the talc, the magnesium stearate and the highly disperse silica are admixed and the mixture is compressed to give tablets of weight 145.0 mg each and active ingredient content 50.0 mg which, if desired, can be provided with breaking notches for finer adjustment of the dose.

Example 132: Coated tablets, each containing 100 mg of active ingredient, for example, 2-cyclohexylamino-4-phenylamino-quinazoline hydrochloride, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.00 g
Lactose	100.00 g
Corn starch	70.00 g
Talc	8.50 g
Calcium stearate	1.50 g
Hydroxypropylmethylcellulose	2.36 g
Shellac	0.64 g
Water q.s.	
Dichloromethane	q.s.

The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened and granulated with a paste prepared from 15 g of corn starch and water (with warming). The granules are dried, and the remainder of the corn starch, the talc and the calcium stearate are added and mixed with the granules. The mixture is compressed to give tablets (weight: 280 mg) and these are coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the coated tablet: 283 mg).

Example 133: Tablets and coated tablets containing another compound of the formula (I) or a pharmaceutically acceptable salt of a compound of the formula (I), for example as in one of Examples 1 to 130, can also be prepared in an analogous manner to that described in Examples 131 and 132.

SEQUENCE LISTING

(1) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1501 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(ix) FEATURE:
(A) NAME/KEY: CDS
(B) LOCATION: 61..1432

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TTAGTTTTGT TCTGAGAACG TTAGAGTTAT AGTACCGTGC GATCGTTCTT CAAGCTGCTA 60

ATG GAC GTC CTC TTC TTC CAC CAG GAT TCT AGT ATG GAG TTT AAG CTT 108
Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu

1 5 10 15

GAG GAG CAT TTT AAC AAG ACA TTT GTC ACA GAG AAC AAT ACA GCT GCT 156
Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala
20 25 30

GCT CGG AAT GCA GCC TTC CCT GCC TGG GAG GAC TAC AGA GGC AGC GTA 204
Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val
35 40 45

GAC GAT TTA CAA TAC TTT CTG ATT GGG CTC TAT ACA TTC GTA AGT CTT 252
Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu
50 55 60

CTT GGC TTT ATG GGC AAT CTA CTT ATT TTA ATG GCT GTT ATG AAA AAG 300
Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
65 70 75 80

CGC AAT CAG AAG ACT ACA GTG AAC TTT CTC ATA GGC AAC CTG GCC TTC 348
Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
85 90 95

TCC GAC ATC TTG GTC GTC CTG TTT TGC TCC CCT TTC ACC CTG ACC TCT 396
Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser
100 105 110

GTC TTG TTG GAT CAG TGG ATG TTT GGC AAA GCC ATG TGC CAT ATC ATG 444
Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met
115 120 125

CCG TTC CTT CAA TGT GTG TCA GTT CTG GTT TCA ACT CTG ATT TTA ATA 492

Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
130 135 140

TCA ATT GCC ATT GTC AGG TAT CAT ATG ATA AAG CAC CCT ATT TCT AAC 540
Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn
145 150 155 160

AAT TTA ACG GCA AAC CAT GGC TAC TTC CTG ATA GCT ACT GTC TGG ACA 588
Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
165 170 175

CTG GGC TTT GCC ATC TGT TCT CCC CTC CCA GTG TTT CAC AGT CTT GTG 636
Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
180 185 190

GAA CTT AAG GAG ACC TTT GGC TCA GCA CTG CTG AGT AGC AAA TAT CTC
684
Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu
195 200 205

TGT GTT GAG TCA TGG CCC TCT GAT TCA TAC AGA ATT GCT TTC ACA ATC 732
Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile
210 215 220

TCT TTA TTG CTA GTG CAG TAT ATC CTG CCT CTA GTA TGT TTA ACG GTA 780
Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
225 230 235 240

AGT CAT ACC AGC GTC TGC CGA AGC ATA AGC TGT GGA TTG TCC CAC AAA
828
Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys
245 250 255

GAA AAC AGA CTC GAA GAA AAT GAG ATG ATC AAC TTA ACC CTA CAG CCA
876
Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro
260 265 270

TCC AAA AAG AGC AGG AAC CAG GCA AAA ACC CCC AGC ACT CAA AAG TGG
924
Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp
275 280 285

AGC TAC TCA TTC ATC AGA AAG CAC AGA AGG AGG TAC AGC AAG AAG ACG
972
Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr
290 295 300

GCC TGT GTC TTA CCC GCC CCA GCA GGA CCT TCC CAG GGG AAG CAC CTA
1020
Ala Cys Val Leu Pro Ala Pro Ala Gly Pro Ser Gln Gly Lys His Leu
305 310 315 320

GCC GTT CCA GAA AAT CCA GCC TCC GTC CGT AGC CAG CTG TCG CCA TCC
1068
Ala Val Pro Glu Asn Pro Ala Ser Val Arg Ser Gln Leu Ser Pro Ser
325 330 335

AGT AAG GTC ATT CCA GGG GTC CCA ATC TGC TTT GAG GTG AAA CCT GAA
1116
Ser Lys Val Ile Pro Gly Val Pro Ile Cys Phe Glu Val Lys Pro Glu
340 345 350

GAA AGC TCA GAT GCT CAT GAG ATG AGA GTC AAG CGT TCC ATC ACT AGA
1164
Glu Ser Ser Asp Ala His Glu Met Arg Val Lys Arg Ser Ile Thr Arg

355 360 365

ATA AAA AAG AGA TCT CGA AGT GTT TTC TAC AGA CTG ACC ATA CTG ATA 1212
Ile Lys Lys Arg Ser Arg Ser Val Phe Tyr Arg Leu Thr Ile Leu Ile
370 375 380

CTC GTG TTC GCC GTT AGC TGG ATG CCA CTC CAC GTC TTC CAC GTG GTG
1260
Leu Val Phe Ala Val Ser Trp Met Pro Leu His Val Phe His Val Val
385 390 395 400

ACT GAC TTC AAT GAT AAC TTG ATT TCC AAT AGG CAT TTC AAG CTG GTA 1308
Thr Asp Phe Asn Asp Asn Leu Ile Ser Asn Arg His Phe Lys Leu Val
405 410 415

TAC TGC ATC TGT CAC TTG TTA GGC ATG ATG TCC TGT TGT CTA AAT CCG 1356
Tyr Cys Ile Cys His Leu Leu Gly Met Met Ser Cys Cys Leu Asn Pro
420 425 430

ATC CTA TAT GGT TTC CTT AAT AAT GGT ATC AAA GCA GAC TTG AGA GCC 1404
Ile Leu Tyr Gly Phe Leu Asn Asn Gly Ile Lys Ala Asp Leu Arg Ala
435 440 445

CTT ATC CAC TGC CTA CAC ATG TCA TGA TTCTCTCTGTG CACCAAAGAG 1452
Leu Ile His Cys Leu His Met Ser *
450 455

AGAAGAAACG TGGTAATTGA CACATAATTT ATACAGAAGT ATTCTGGAT
1501

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 457 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Asp Val Leu Phe Phe His Gln Asp Ser Ser Met Glu Phe Lys Leu
1 5 10 15

Glu Glu His Phe Asn Lys Thr Phe Val Thr Glu Asn Asn Thr Ala Ala
20 25 30

Ala Arg Asn Ala Ala Phe Pro Ala Trp Glu Asp Tyr Arg Gly Ser Val
35 40 45

Asp Asp Leu Gln Tyr Phe Leu Ile Gly Leu Tyr Thr Phe Val Ser Leu
50 55 60

Leu Gly Phe Met Gly Asn Leu Leu Ile Leu Met Ala Val Met Lys Lys
65 70 75 80

Arg Asn Gln Lys Thr Thr Val Asn Phe Leu Ile Gly Asn Leu Ala Phe
85 90 95

Ser Asp Ile Leu Val Val Leu Phe Cys Ser Pro Phe Thr Leu Thr Ser
100 105 110

Val Leu Leu Asp Gln Trp Met Phe Gly Lys Ala Met Cys His Ile Met
115 120 125

Pro Phe Leu Gln Cys Val Ser Val Leu Val Ser Thr Leu Ile Leu Ile
130 135 140

Ser Ile Ala Ile Val Arg Tyr His Met Ile Lys His Pro Ile Ser Asn
145 150 155 160

Asn Leu Thr Ala Asn His Gly Tyr Phe Leu Ile Ala Thr Val Trp Thr
165 170 175

Leu Gly Phe Ala Ile Cys Ser Pro Leu Pro Val Phe His Ser Leu Val
180 185 190

Glu Leu Lys Glu Thr Phe Gly Ser Ala Leu Leu Ser Ser Lys Tyr Leu
195 200 205

Cys Val Glu Ser Trp Pro Ser Asp Ser Tyr Arg Ile Ala Phe Thr Ile
210 215 220

Ser Leu Leu Leu Val Gln Tyr Ile Leu Pro Leu Val Cys Leu Thr Val
225 230 235 240

Ser His Thr Ser Val Cys Arg Ser Ile Ser Cys Gly Leu Ser His Lys
245 250 255

Glu Asn Arg Leu Glu Glu Asn Glu Met Ile Asn Leu Thr Leu Gln Pro
260 265 270

Ser Lys Lys Ser Arg Asn Gln Ala Lys Thr Pro Ser Thr Gln Lys Trp
275 280 285

Ser Tyr Ser Phe Ile Arg Lys His Arg Arg Arg Tyr Ser Lys Lys Thr
290 295 300